Helicobacter pylori Persistence: an Overview of Interactions between *H. pylori* and Host Immune Defenses

Holly M. Scott Algood[1] and Timothy L. Cover[1,2,3]*

Departments of Medicine[1] and Microbiology and Immunology,[2] Vanderbilt University School of Medicine, and Veterans Affairs Tennessee Valley Healthcare System,[3] Nashville, Tennessee

INTRODUCTION

The gram-negative bacterium *Helicobacter pylori* persistently colonizes the human stomach (34, 145, 153, 217). *H. pylori* colonization of the stomach elicits humoral and cellular immune responses (28, 52, 129, 180), which in most cases do not result in bacterial clearance. In the absence of antibiotic therapy, *H. pylori* can persist in the human stomach for decades or for an entire lifetime (116). *H. pylori* is widespread throughout the world and is present in about 50% of the global human population (178, 226). *H. pylori*-induced gastric inflammation does not cause symptoms in most infected persons (56) but is associated with an increased risk for development of duodenal ulcer disease, gastric ulcer disease, gastric adenocarcinoma, and gastric lymphoma (45, 179, 183, 217, 233). In this review, we examine innate and adaptive immune responses to *H. pylori* and discuss mechanisms by which *H. pylori* evades immune clearance.

ANTIBACTERIAL PROPERTIES OF THE HUMAN STOMACH

Humans ingest many microorganisms each day, but most cannot successfully colonize the stomach. One of the most important antibacterial properties of the human stomach is its acidic pH. Under fasting conditions, the human gastric luminal pH is <2, which prevents the proliferation of bacteria within the gastric lumen. Within the gastric mucus layer overlying gastric epithelial cells, a pH gradient exists, ranging from a pH of about 2 at the luminal surface to a pH of between 5 and 6 at the epithelial cell surface (185, 225). After entering the stomach, *H. pylori* penetrates the gastric mucus layer (203) and thereby encounters a less acidic environment than that which is present within the gastric lumen. *H. pylori* typically does not traverse the epithelial barrier (97), and it is classified as a noninvasive bacterial organism. Within the gastric mucus layer, most *H. pylori* organisms are free living, but some organisms attach to the apical surface of gastric epithelial cells and may occasionally be internalized by these cells (10, 97, 119, 173).

Multiple factors produced by the gastric mucosa limit the proliferation of bacteria (Fig. 1). Antibacterial peptides, including β-defensins 1 and 2 and LL-37, are active against many different species of bacteria (74, 94). Lactoferrin inhibits bacterial growth by restricting the availability of extracellular Fe^{3+} (133) and can have direct effects on bacterial membrane per-

* Corresponding author. Mailing address: Division of Infectious Diseases, A2200 Medical Center North, Vanderbilt University School of Medicine, Nashville, TN 37232. Phone: (615) 322-2035. Fax: (615) 343-6160. E-mail: timothy.L.cover@vanderbilt.edu.
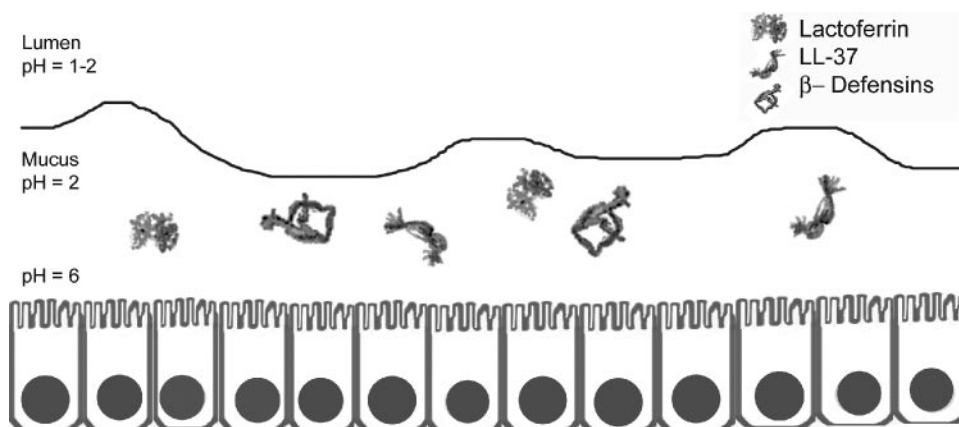
FIG. 1. Antibacterial properties of the stomach. The stomach is intrinsically resistant to bacterial colonization. Factors which contribute to this resistance include gastric acidity, lactoferrin, and antibacterial peptides (LL-37, β-defensin 1, and β-defensin 2). The gastric epithelial layer constitutes a physical barrier that prevents entry of bacteria into the gastric mucosa. Ribbon diagrams of lactoferrin, β-defensins, and LL-37 are derived from published structures (24, 200, 218).

meability (13, 175, 253). Lactoferricin, a peptide derived from lactoferrin, also has antimicrobial properties (80). Lysozyme can degrade the peptidoglycan of many bacterial species. Surfactant protein D is capable of aggregating many different types of microorganisms in a calcium-dependent and lectin-specific manner (114, 158, 164). Finally, specific components of human gastric mucin can inhibit bacterial growth; alpha-1,4-GluNAC-capped O-glycans inhibit biosynthesis of cholesteryl-α-D-glucopyranoside, a component of the *H. pylori* cell wall (112).

Toll-like receptors (TLRs) are present on the surface of gastric epithelial cells and can recognize pathogen-associated molecular patterns (PAMPs) (21, 201, 216). If bacteria invade and penetrate the gastric epithelial barrier, the alternate pathway of complement is activated, and invading bacteria encounter macrophages and neutrophils. Since most *H. pylori* organisms localize within the gastric mucus layer and do not invade gastric tissue, contact between *H. pylori* and phagocytic cells probably occurs infrequently unless there are disruptions in the gastric epithelial barrier.

The antibacterial properties of the human stomach described above prevent most bacterial species from colonizing the stomach. Based on the high prevalence of *H. pylori* in humans throughout the world, it may be presumed that *H. pylori* possesses mechanisms to overcome these innate host defenses.

H. PYLORI FACTORS THAT CONTRIBUTE TO GASTRIC COLONIZATION

The capacity of *H. pylori* to colonize the human stomach can be attributed to the production of specific bacterial products (Fig. 2). Numerous *H. pylori* components have been designated colonization factors based on the demonstration that null mutant strains defective in the production of these factors are impaired in the ability to colonize the stomach in animal models. For example, *H. pylori* null mutant strains defective in production of urease or flagella are unable to colonize animal models (59, 62). Urease hydrolyzes urea to yield ammonium ions and thereby contributes to the acid resistance of *H. pylori*

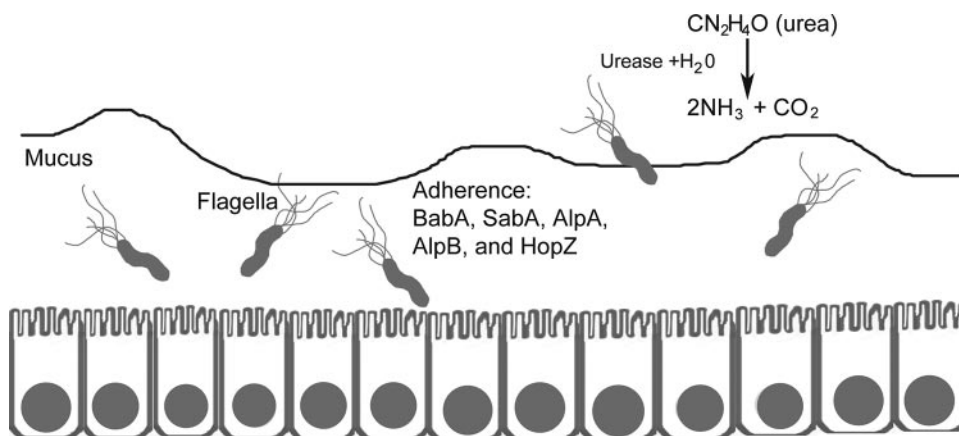FIG. 2. Colonization factors of *H. pylori*. Multiple bacterial factors contribute to the ability of *H. pylori* to colonize the stomach. Urease contributes to the acid resistance of *H. pylori*. Flagella permit bacterial motility, which allows bacterial penetration of the mucus layer. Several outer membrane proteins, including BabA, SabA, AlpA, AlpB, and HopZ, can mediate bacterial adherence to gastric epithelial cells.

(144). Flagella confer the property of motility and enable *H. pylori* to penetrate the gastric mucus layer. In a recent signature-tagged mutagenesis analysis, 47 *H. pylori* genes were found to be essential for colonization of the Mongolian gerbil stomach but not essential for growth of *H. pylori* in vitro (111). Probably many other *H. pylori* factors are also required for colonization of the stomach.

Multiple *H. pylori* outer membrane proteins, including BabA, SabA, AlpA, AlpB, and HopZ, can mediate *H. pylori* adherence to gastric epithelial cells (Fig. 2). Attachment of *H. pylori* to gastric epithelial cells results in activation of numerous signaling pathways (87) and permits efficient delivery of toxins or other effector molecules into the cells. Studies in an animal model indicate that attachment of *H. pylori* to epithelial cells influences the development of gastric mucosal inflammation, production of autoantibodies, and parietal cell loss (90).

H. pylori outer membrane proteins and other surface components are likely targets for recognition by host immune defenses. One mechanism by which *H. pylori* evades immune recognition may involve a form of antigenic disguise in which the bacteria are coated with host proteins. For example, *H. pylori* PgbA and PgbB proteins bind plasminogen, and the bacteria can thereby be coated with this host protein (108). Other mechanisms for evading immune recognition may involve phase variation and antigenic variation of surface components. Phase variation has been reported for multiple *H. pylori* surface components, including outer membrane proteins and lipopolysaccharide (LPS) antigens (14, 198, 210, 241). Genetic rearrangements contribute to antigenic variation in CagY (16), and intragenomic recombination may contribute to antigenic variation in outer membrane proteins (210).

LPS from most bacterial organisms serves as a potent signal for development of an inflammatory response. An important *H. pylori* adaptation is the synthesis of LPS that is less proinflammatory than LPSs from many other gram-negative species (114, 157, 181). In comparison to LPS from *Escherichia coli* or *Salmonella enterica* serovar Typhimurium, *H. pylori* LPS has approximately 500-fold-lower endotoxic activity (162), and its ability to stimulate macrophage production of proinflammatory cytokines, nitric oxide, and prostaglandins is relatively weak (35, 181). The low biological activity of *H. pylori* LPS is attributable to modifications of its lipid A component (157, 162). *H. pylori* strains commonly express LPS O antigens that are structurally related to Lewis blood group antigens found on human cells (19, 154). This similarity in structure between *H. pylori* LPS and Lewis blood group antigens may represent a form of molecular mimicry or immune tolerance that permits *H. pylori* LPS antigens to be shielded from immune recognition because of similarity to "self" antigens.

Many *H. pylori* strains contain a 40-kb region of chromosomal DNA known as the *cag* pathogenicity island (PAI) (5, 40). Some strains contain an incomplete *cag* PAI (less than 40 kb in size), and in other strains the *cag* PAI is completely absent (40, 166). One product of the *cag* pathogenicity island, CagA, is translocated into gastric epithelial cells and induces numerous alterations in cellular signaling (18, 98, 171, 204, 214). Multiple other products of the *cag* pathogenicity island have a role in secretion of CagA and in altering gene transcription in gastric epithelial cells (5, 40, 71, 87, 205). In comparison to *cag* PAI-negative *H. pylori* strains, *cag* PAI-positive strains stimulate gastric epithelial cells to produce high levels of proinflammatory cytokines such as interleukin-8 (IL-8) (5, 38, 71, 87, 125, 161, 205). Gastric cancer and peptic ulcer disease occur more commonly in persons infected with *cag* PAI-positive strains (particularly those strains containing an intact 40-kb *cag* PAI) than in persons infected with *cag* PAI-negative strains (33, 70, 166, 236).

Several *H. pylori* factors are known to interact directly with immune cells and modulate immune responses to *H. pylori*. These factors include a secreted toxin (VacA) (37, 46, 77, 219), neutrophil-activating protein (HP-NAP or NapA) (68, 197), arginase (83, 256), urease (93, 139, 140), Hsp60 (a GroEL heat shock protein) (81), SabA (235), HcpA (53), CagA (170, 234), and a proinflammatory peptide designated Hp(2-20) (29). Several of these factors act on multiple different types of immune cells. For example, VacA alters the function of T lymphocytes, B cells, macrophages, and mast cells (37, 49, 77, 152, 219, 220, 258), and HP-NAP acts on neutrophils, mast cells, and monocytes (155, 156, 197). The activities of *H. pylori* factors that interact directly with immune cells will be discussed in greater detail below.

IMMUNE RESPONSE TO *H. PYLORI* IN HUMANS

Acute Infection

There have been several reports of acute *H. pylori* infection in humans, and these provide insight into the immune responses to *H. pylori* that occur within the first few days after infection. Soon after the discovery of *H. pylori*, two volunteers ingested cultures of the organism (143, 159, 160). Both volunteers developed nausea, vomiting, or fever within 10 days after ingesting *H. pylori*, and gastric biopsies revealed mucosal inflammation in both volunteers. By 2 weeks postinfection, a sharp rise in the gastric pH to about 7 was detected in one of the volunteers. In 1979, a group of 17 volunteers were probably inadvertently infected with *H. pylori* (85, 191), and these persons also developed hypochlorhydria in association with gastric mucosal inflammation. Further insight comes from a case in which an endoscopist reported a syndrome of cramping epigastric pain, accompanied by transient fasting achlorhydria and acute neutrophilic gastritis, about 5 days after infection with *H. pylori* (208). Within 14 days after infection, this individual developed an *H. pylori*-specific immunoglobulin M (IgM) and IgA immune response.

More recently, 20 human volunteers were experimentally infected with 10^4 to 10^{10} CFU of an *H. pylori* strain (86). Symptoms occurred most frequently during the second week after infection and included dyspepsia (in >50% of subjects), headaches, anorexia, abdominal pain, belching, and halitosis. Gastric biopsies performed 2 weeks after infection showed infiltration of lymphocytes and monocytes, along with significantly increased expression of IL-1β, IL-8, and IL-6 in the gastric antrum (86). Four weeks after infection, the numbers of gastric $CD4^+$ and $CD8^+$ T cells were increased compared to preinfection levels, indicating the development of an early adaptive immune response (168). These cases provide evidence that gastric inflammation develops within a short period of time after *H. pylori* infection and that the initial colonization of the stomach by *H. pylori* frequently results in upper gastro-

intestinal symptoms. Either innate immune responses to *H. pylori* or early adaptive immune responses could account for the gastric mucosal inflammatory responses and symptoms that accompany acute infection.

Chronic Infection

Gastric mucosal biopsies from humans who are persistently infected with *H. pylori* reveal an increased concentration of various types of leukocytes compared to biopsies from uninfected humans (45, 55). This inflammatory response to *H. pylori* has been termed "chronic superficial gastritis" (55, 243). Lymphocytes (both T cells and B cells), macrophages, neutrophils, mast cells, and dendritic cells (DCs) are usually present (27, 55, 222). CD4$^+$ T cells are typically more abundant than CD8$^+$ T cells (22, 132, 146, 184). CD4$^+$/CD25^{hi} regulatory T cells expressing FOXP3 are present in higher numbers in the gastric mucosa of *H. pylori*-infected persons than in uninfected persons, and these are presumed to play an important role in regulating the inflammatory response (130, 131). Various cell types, including B cells and CD4$^+$ cells, sometimes organize into lymphoid follicles (228). The chronic gastric mucosal inflammatory response to *H. pylori* probably reflects the combined effects of a cellular immune response and an ongoing stimulation of an innate immune response.

In contrast to the intestine, the stomach does not contain Peyer's patches or M cells (165). Therefore, there is some uncertainty about the location where priming of the immune response to *H. pylori* occurs. Gastric epithelial cells up-regulate expression of major histocompatibility complex (MHC) class II and costimulatory molecules during *H. pylori* infection (17, 255), and potentially these cells have a role in antigen presentation. Monocytes, macrophages, and dendritic cells in the lamina propria of the gastric mucosa also may play important roles in antigen presentation (115, 222, 240). Alternatively, priming of the immune response to *H. pylori* may occur within lymph nodes draining the stomach or may occur at intestinal sites in response to *H. pylori* antigens or intact organisms that are shed from the stomach.

H. pylori-specific CD4$^+$ T cells are detectable in the gastric mucosae of *H. pylori*-infected persons but not uninfected persons (52, 54, 132). One study reported that about 15% of CD4$^+$ T-cell clones isolated from the stomachs of *H. pylori*-infected persons were *H. pylori* specific, whereas the other T-cell clones did not proliferate in response to antigens in *H. pylori* lysate (52). Some T-cell clones from *H. pylori*-infected patients recognize epitopes on parietal cell H$^+$,K$^+$-ATPase (9), and it has been suggested that recognition of H$^+$,K$^+$-ATPase by gastric T cells may contribute to the development of autoimmune gastritis (51).

Levels of numerous cytokines, including gamma interferon (IFN-γ), tumor necrosis factor (TNF), IL-1β, IL-6, IL-7, IL-8, IL-10, and IL-18, are increased in the stomachs of *H. pylori*-infected humans compared to uninfected humans (47, 126). IL-4 has not been detected in the gastric mucosae of most *H. pylori*-infected persons (110, 126, 184). The Th1-defining cytokine, IFN-γ, is expressed by a higher proportion of gastric T cells from *H. pylori*-infected persons than gastric T cells from uninfected persons (22, 91, 110, 126, 211). In one study, 83% of *H. pylori*-specific gastric T-cell clones produced IFN-γ but not

IL-4 upon stimulation with *H. pylori* antigens, compared to 17% of clones that produced IL-4 (22, 52). Based on the relative abundance of IFN-γ-producing T cells and the relative scarcity of IL-4-producing gastric T cells in the setting of *H. pylori* infection, it has been concluded that *H. pylori* infection leads to a Th1-polarized response (22, 211). In the setting of *H. pylori* infection, multiple cytokines in the gastric mucosa (including TNF, IFN-γ, IL-1β, IL-6, IL-8, and IL-18) are predicted to have proinflammatory effects, whereas IL-10 is an immunoregulatory cytokine that may limit the inflammatory response.

A humoral immune response to *H. pylori* is elicited in nearly all *H. pylori*-infected humans (180). In a study of *H. pylori*-infected human volunteers, *H. pylori*-specific serum IgM antibodies were present by 4 weeks postinfection (168). Serum IgA and IgG antibodies in persons with chronic *H. pylori* infection are directed toward many different *H. pylori* antigens (147, 180). Antibody-secreting cells producing *H. pylori*-specific IgA or IgM antibodies are detectable in the gastric mucosae of *H. pylori*-infected persons (147), and secretory IgA antibodies to *H. pylori* are detectable in gastric juice, which suggests that *H. pylori* infection elicits a local secretory IgA response in the stomach (96, 147).

Factors Modulating the Immune Response to *H. pylori* in Humans

The gastric mucosal inflammatory response to *H. pylori* in humans may be modulated by characteristics of the *H. pylori* strain. Infection with *H. pylori* strains containing the *cag* PAI is typically associated with a more severe inflammatory response than that which accompanies infection with *cag* PAI-negative strains (33, 230). Similarly, *H. pylori* strains containing type s1/m1 *vacA* alleles, containing a gene of unknown function known as jhp0917/0918 (*dupA*), and expressing certain outer membrane proteins (BabA and HopH [OipA]) are associated with an enhanced inflammatory response (128, 137, 186, 252).

The gastric inflammatory response to *H. pylori* also may be modulated by characteristics of the human host. *H. pylori*-associated gastric inflammation in adults is characterized by infiltration of mononuclear cells and neutrophils, whereas in children the inflammatory response often is predominantly lymphocytic with relatively few neutrophils (246). Adults who are persistently colonized with *H. pylori* for many decades may develop atrophic gastritis (an inflammatory process characterized by loss of glandular structures and parietal cells in the gastric mucosa), which is considered a preneoplastic lesion (45, 117).

No immunodeficiency diseases are known to result in enhanced severity of *H. pylori*-associated inflammation. For example, gastric inflammation is not more severe in *H. pylori*-infected humans with IgA deficiency than in immunocompetent hosts (36). However, single-nucleotide polymorphisms in several genes encoding proinflammatory cytokines can influence the clinical outcome of *H. pylori* infection (Table 1). Polymorphisms that result in elevated levels of IL-1β and TNF-α and reduced levels of IL-10 have been associated with an increased risk of atrophic gastritis and gastric cancer (64, 66, 101, 134, 232, 248). A polymorphism in the promoter region of IL-1 receptor antagonist that leads to reduced expression of IL-1

TABLE 1. Genetic polymorphisms in cytokine-encoding genes which influence the clinical course of *H. pylori* infection in humans

Gene product	Polymorphism(s)	Postulated effect of polymorphism	Reference(s)
IL-1β	IL-1B-31C, IL-1B-511T	Increased expression of IL-1β, which induces expression of proinflammatory cytokines and inhibits acid secretion	63–66, 134, 135
IL-1RA	IL-1RN*2	Reduced expression of IL-1 receptor agonist, which increases IL-1β activity	135
IL-2	IL-2-330T	Reduced IL-2 expression	232
IL-10	IL-10 haplotype ATA	Reduced expression of IL-10, which increases proinflammatory cytokine activity	66
TNF	TNF-A-308A	Increased TNF expression, which induces expression of proinflammatory cytokines and inhibits acid secretion	66, 134

receptor antagonist has also been associated with an increased incidence of atrophic gastritis and gastric cancer (64, 135, 187). The exact mechanisms by which these polymorphisms affect the risk for gastric cancer are not yet completely understood. Some of the TNF-α and IL-10 polymorphisms associated with increased risk for gastric cancer are considered proinflammatory genotypes (66, 134), and IL-1β is known to be a potent inhibitor of gastric acid secretion (254). These polymorphisms may predispose individuals to develop gastric atrophy and gastric cancer by pathways involving enhancement in the severity of gastric inflammation and a reduction in gastric acid secretion (254).

Although *H. pylori* is very successful in evading immune clearance, it is possible that the immune response is sometimes successful in clearing *H. pylori* from the stomach. The frequency with which *H. pylori* is cleared by the immune response is not known. In regions of the world with a high incidence of *H. pylori* infection, reinfection occurs commonly following *H. pylori* eradication (213), which suggests that a protective immune response develops infrequently in *H. pylori*-infected persons.

INTERACTIONS BETWEEN *H. PYLORI* AND HOST DEFENSES IN ANIMAL MODELS

H. pylori Infection of Wild-Type Animals

Several animal models of *H. pylori* infection have been developed, utilizing mice, Mongolian gerbils, guinea pigs, rats, ferrets, beagle dogs, cats, gnotobiotic piglets, or nonhuman primates (reviewed in references 174 and 245). The use of nonhuman primate models is of particular interest because of the close relatedness of these animals to humans. The rhesus monkey can be experimentally infected with *H. pylori*, and a large proportion of monkeys in certain colonies are naturally infected with *H. pylori* (57, 58, 148, 209). Histopathological changes that occur in the gastric mucosae of monkeys in response to *H. pylori* infection are similar to the changes that occur in *H. pylori*-infected humans (148). However, *H. pylori*-associated peptic ulceration and gastric adenocarcinoma have not been described in nonhuman primate models (148).

Mongolian gerbils can be experimentally infected with *H. pylori* and develop gastric inflammation characterized by infiltration of mononuclear cells and neutrophils (149, 172, 247). An attractive feature of the Mongolian gerbil model is that these animals may develop gastric mucosal ulceration or gas-

tric adenocarcinoma in response to *H. pylori* infection (73, 100, 172, 244), and they thus provide a model for two important *H. pylori*-associated diseases that occur in humans. Several studies suggest that products of the *H. pylori cag* pathogenicity island contribute to gastric pathology in the gerbil model (105, 172, 192). Limitations of this model include the relative paucity of gerbil-specific immunologic reagents and the fact that Mongolian gerbils are outbred.

The mouse model is frequently utilized because of low cost, availability of relevant reagents, and the potential for development of knockout mice (142). *H. pylori* can persistently colonize the stomachs of wild-type mice for periods of at least 15 months. However, wild-type mice do not develop gastric mucosal ulceration or gastric adenocarcinoma in response to *H. pylori*. One limitation of the mouse model is that only a few human isolates of *H. pylori* have been successfully adapted to permit efficient colonization of the mouse stomach (20). Infant mice and certain types of knockout mice (e.g., IL-12 knockout mice) seem to be more permissive hosts than are wild-type adult mice and tolerate infection with a broader range of *H. pylori* strains (89, 99). A different *Helicobacter* species, *H. felis*, also can colonize conventional inbred mice and causes more severe gastric inflammation than does *H. pylori* (196). However, *H. felis* does not express several important *H. pylori* virulence factors (249).

The gastric mucosal inflammation that develops in wild-type mice infected with *H. pylori* consists primarily of lymphocytes and other mononuclear cells. Most of the infiltrating cells are CD4$^+$ T cells, but CD8$^+$ T cells, B cells, dendritic cells, and monocytes are also present (167, 199, 207, 237). The intensity of inflammation that develops in *H. pylori*-infected mice is relatively mild compared to that which develops in *H. pylori*-infected humans and is also relatively mild compared to that which develops in *H. pylori*-infected Mongolian gerbils (121). Neutrophils are typically present in the gastric mucosae of *H. pylori*-infected humans (194, 246) and gerbils (100) but are less commonly observed in the gastric mucosae of *H. pylori*-infected mice (138).

C57BL/6 mice have been commonly used for studies of *H. pylori*. Gastric levels of IFN-γ, IL-12, TNF, and IL-6 are increased in *H. pylori*-infected C57BL/6 mice compared to uninfected mice, whereas gastric levels of IL-4 are not increased in response to *H. pylori* infection (150, 212). Upon antigen stimulation ex vivo, splenocytes from *H. pylori*-infected C57BL/6 mice produce substantially more IFN-γ than IL-4 (107, 127,

TABLE 2. *H. pylori* infection of mouse knockout models[a]

Knockout model (mouse strain[s])	*H. pylori* strain	Bacterial density compared to WT	Inflammation compared to control	Reference(s)
NOS2$^{-/-}$ (C57BL/6)	SS1	Similar colonization	More severe gastritis	32
Gp91^{phox}/NOS2$^{-/-}$ (C57BL/6)	SS1	Reduced colonization	More severe gastritis	32
SCID (B- and T-cell deficient) (C57BL/6)	SS1	Greater colonization	No gastric inflammation	61
μ-MT (B-cell deficient) (C57BL/6)	SS1	Reduced colonization	More severe gastritis	3
MHC class I KO (C57BL/6)	SS1	Greater colonization	ND	177
MHC class II KO (C57BL/6)	SS1	Greater colonization	ND	177
IFN-γ KO (C57BL/6)	SM326	ND	No gastric inflammation	207
IFN-γ KO (C57BL/6)	CPY2052	Greater colonization	No gastric inflammation	199, 251
IFN-γ KO (C57BL/6 and BALB/c)	SM326	More frequent recovery of bacteria	ND	109
IRF-1 KO (C57BL/6)	SS1	Greater colonization	No gastritis	212
IL-4 KO (C57BL/6)	SM326	ND	More severe gastritis	207
IL-4 KO (C57BL/6 and BALB/c)	SM326	Similar colonization	ND	109
IL-4 KO (C57BL/6)	SS1	Similar colonization	Similar degree of gastritis	42
IL-4 Tg (IL-4 overexpression) (C3H)	SS1	Similar colonization	Similar degree of gastritis	42
IL-10 KO (IL-10$^{+/-}$, 129 × C57BL/6)	SS1	Reduced colonization	More severe gastritis	43
IL-12 KO (C57BL/6)	SS1	Similar colonization	Similar degree of gastritis	2
FasL KO (C57BL/6)	SS1	Similar colonization	Similar degree of gastritis	107
TNF KO (C57BL/6)	CPY2052 and KP142	Greater colonization	Similar degree of gastritis	251
TNF receptor KO (C57BL/6)	Six clinical isolates of *H. pylori*	ND	Similar degree of gastritis	229

[a] This table summarizes the results of selected studies in which transgenic mouse models were infected with *Helicobacter pylori*. WT, wild type; ND, not determined; KO, knockout.

207). These patterns of cytokine expression are indicative of a predominantly Th1 response, which is similar to the response which occurs in *H. pylori*-infected humans.

There is variability among different strains of inbred mice in susceptibility to *H. pylori* infection (138, 231) and in host responses to *H. pylori*. Inbred mice are known to have default T-helper responses, and therefore, the genetic backgrounds of inbred mice may influence the T-cell response to *H. pylori*. C57BL/6 mice have a default Th1 response, whereas BALB/c mice have a default Th2 response (113). This difference may be a factor that helps to explain why BALB/c mice are relatively resistant to *H. pylori* colonization and why *H. pylori*-infected BALB/c mice develop relatively mild gastric inflammation compared to *H. pylori*-infected C57BL/6 mice (109, 196).

H. pylori Infection of Knockout Mice

Mouse knockout models have served as valuable tools for investigating the roles of various components of the immune response to *H. pylori*. Features of *H. pylori* infection in selected mouse knockout models are discussed below, and a summary of the data is shown in Table 2. As noted above, inbred mice are known to have default T-helper responses, and consequently, the genetic backgrounds of mouse strains can potentially influence the results of knockout mouse studies. Most studies of *H. pylori* infection in knockout mice have been performed with C57BL/6 animals, which have a default Th1 response.

SCID (severe combined immunodeficient) mice lack mature T and B lymphocytes due to a defective capacity to express rearranged antigen receptors and are therefore deficient in both humoral and cell-mediated immunity. SCID mice can be successfully colonized by *H. pylori*, but these mice develop minimal gastric inflammation in response to infection (61). This indicates that an adaptive immune response is required

for development of chronic gastric inflammation in response to *H. pylori* and also indicates that gastric inflammation is not required in order for *H. pylori* to persistently colonize the stomach. If *H. pylori*-infected SCID mice receive splenocytes from uninfected C57BL/6 mice through adoptive transfer, the recipient SCID mice develop severe gastric inflammation characterized by a neutrophilic infiltrate (61). The gastritis that develops in *H. pylori*-infected SCID recipient mice is more severe than that which occurs in *H. pylori*-infected C57BL/6 mice (61). The transfer of splenocytes to SCID mice potentially induces a severe form of gastritis due to the absence of regulatory cells in the SCID mice (61, 182).

μ-MT (B-cell-deficient) mice infected with *H. pylori* develop gastritis that is more severe than that which occurs in wild-type mice, and subsequently *H. pylori* infection is cleared from the stomachs of the B-cell-deficient mice (3). There are several possible reasons why *H. pylori*-induced gastritis may be more severe in B-cell-deficient mice than in wild-type mice. For example, antibodies produced by wild-type mice may engage the inhibitory IgG receptor (FcγRIIb) on leukocytes and increase expression of anti-inflammatory cytokines such as IL-10 (3).

In comparison to *H. pylori*-infected wild-type mice, *H. pylori*-infected mice with defects in IFN-γ expression (IFN-γ$^{-/-}$ mice or interferon response factor 1$^{-/-}$ mice) develop less severe gastric inflammation and have higher bacterial colonization densities (2, 169, 199, 207, 212, 251). This suggests that IFN-γ contributes to increased severity of *H. pylori*-induced gastric inflammation while also contributing to reducing bacterial colonization. In support of this view, *H. pylori*-infected SCID mice reconstituted with splenocytes that express IFN-γ developed more severe gastritis than did mice reconstituted with IFN-γ-deficient splenocytes (60). IFN-γ may indirectly modulate the severity of gastritis by activating macrophages to secrete proin-

flammatory cytokines and also may down-regulate the expression of anti-inflammatory factors such as the anti-inflammatory cytokine transforming growth factor β (215).

In comparison to *Helicobacter*-infected mice that express IL-10, infected IL-10$^{-/-}$ mice develop more severe gastritis (26, 43). IL-10 is known to be a potent anti-inflammatory and immunoregulatory cytokine, and therefore it seems likely that IL-10 has a role in down-regulating *H. pylori*-induced inflammation (43). One study reported that *H. pylori*-infected IL-4$^{-/-}$ mice developed more severe gastritis than did *H. pylori*-infected wild-type C57BL/6 mice (207). Similarly, *H. felis*-infected IL-4$^{-/-}$ mice developed significantly more severe gastric inflammation than did *H. felis*-infected IL-4$^{+/+}$ mice (151). Although the results of studies analyzing IL-4$^{-/-}$ mice have not been entirely uniform (42, 109), these data suggest that both IL-10 and IL-4 have a role in down-regulating gastric inflammation (26, 72, 151, 207, 257).

A general theme that emerges from studies of *H. pylori* in mouse models is that there is a reciprocal relationship between the intensity of gastric mucosal inflammation and bacterial load (or colonization density) (32, 43, 61, 188, 199, 251). For example, IFN-γ$^{-/-}$ mice have relatively high bacterial loads and mild gastritis, whereas IL-10$^{-/-}$ mice have relatively low bacterial loads and severe gastritis (43). As will be discussed later in this review, these observations are relevant to understanding the immunologic basis for protective immunity to *H. pylori*.

Th1 and Th2 Responses in Mice

The data described above, involving experiments with various knockout mice, suggest that expression of IFN-γ (a Th1 cytokine) contributes to enhanced gastric inflammation, whereas expression of certain Th2 cytokines (IL-10 and possibly IL-4) contributes to diminished inflammation. To investigate further the role of Th1 and Th2 responses in modulating gastric inflammation, C57BL/6 mice were initially infected with a nematode that induces a strong Th2 response and then were challenged with *H. felis* (72). In comparison to mice infected with *H. felis* alone, the mice coinfected with *H. felis* and the nematode had reduced gastric expression of Th1 cytokines (IFN-γ, TNF, and IL-1β), increased gastric expression of Th2 cytokines (IL-4, IL-10, and transforming growth factor β), and reduced gastric inflammatory scores (72). These data provide support for the hypothesis that a Th2-polarized response down-regulates the severity of *H. pylori*-induced gastric inflammation.

Several cytokines affect the expression of gastric hormones that control gastric acid secretion. Expression of gastrin, a hormone that stimulates gastric acid secretion, is stimulated by IFN-γ (257), and expression of somatostatin, a hormone that inhibits gastric acid secretion, is stimulated by IL-4 and inhibited by IFN-γ and TNF (25, 257). Increased expression of IFN-γ (a Th1 response) is expected to result in increased gastrin production, whereas expression of IL-4 (a Th2 response) is expected to result in increased somatostatin production and reduced gastrin secretion. One study used a mouse model of *H. felis* infection to investigate the effects of IL-4-induced alterations on gastrin and somatostatin expression (257). As expected, administration of IL-4 resulted in increased somatostatin expression and reduced gastrin expres-

sion. These changes were accompanied by a reduction in the severity of *H. felis*-induced gastritis. The modulatory effects of IL-4 on the severity of gastric inflammation were observed in *H. felis*-infected wild-type mice but not in infected somatostatin knockout mice, which suggested that the IL-4-induced alterations in inflammation were mediated through effects of IL-4 on somatostatin production by D cells (257).

Role of Regulatory T Cells

The gastric mucosal inflammatory response to *H. pylori* may be regulated in part by regulatory T cells (Tregs) (CD25$^+$ CD45RB^{lo} T cells). CD4$^+$/CD25$^+$ Tregs can suppress cytokine production and proliferation of other T cells (118). One recent study investigated the role of Tregs in a murine model of *H. pylori*-induced gastritis by reconstituting athymic C57BL/6 nude mice (T-cell-deficient nu/nu mice) with either lymph node cells containing CD25$^+$ cells or lymph node cells depleted of CD25$^+$ cells, 3 weeks prior to *H. pylori* infection (188). In mice reconstituted with a cell population depleted of Tregs, a relatively severe gastritis occurred by 6 weeks postinfection compared to that which occurred in mice reconstituted with a nonsorted T-cell population (containing both CD25$^+$ and CD25$^-$ T cells). The mice reconstituted with a T-cell population lacking CD25$^+$ cells developed a stronger Th1 response, characterized by increased numbers of CD4$^+$ T cells in the mucosa and increased IFN-γ production compared to mice reconstituted with an unsorted T-cell population (188). These data indicate that Tregs have an important role in regulating the gastric mucosal inflammatory response to *H. pylori*.

Protective Immunity in Animal Models

Protective immunity to *H. pylori* may be defined as either (i) immunity that protects against *H. pylori* colonization of the stomach or (ii) an immune response that results in eradication of an established infection. Both prophylactic *H. pylori* immunization (to prevent future infection) and therapeutic immunization (to eradicate an established infection) have been successfully accomplished in animal models (50, 106, 142, 195).

Several early studies suggested that protection might be mediated by *Helicobacter*-specific antibodies (30, 48, 69, 122). Subsequently, it was shown that immunization of μ-MT mice (which are unable to produce antibodies) or IgA-deficient mice can result in protective immunity against *H. pylori* or *H. felis* infection (3, 31, 67, 76, 84, 221). Therefore, there is now a general consensus that *H. pylori*-specific antibodies are not required for protective immunity.

Cellular immune responses seem to have an important role in protective immunity against *H. pylori*. Mice deficient in CD8$^+$ T cells (MHC class I$^{-/-}$ mice) can be successfully immunized and protected against colonization with *H. pylori* (177), whereas mice deficient in CD4$^+$ T cells (MHC class II$^{-/-}$ mice) were not protected by prophylactic immunization against *H. pylori* (177). CD4$^+$ T cells from *H. felis*-immunized mice can mediate protective immunity if adoptively transferred into immunodeficient Rag1$^{-/-}$ mice (84). These data suggest that CD4$^+$ T cells, but not CD8$^+$ cells, are necessary for protection (67, 177).

Several lines of evidence suggest that Th2-type responses

might be required for protective immunity against *H. pylori*. Specifically, persistent *H. pylori* infections in humans and mice typically result in Th1-polarized responses, whereas successful *Helicobacter* immunization of animals typically results in Th2-polarized responses (1, 50). In addition, adoptive transfer of Th2 cells from *H. felis*-infected C57BL/6 mice into infected C57BL/6 mice significantly reduced the bacterial load compared to when Th1 cells were adoptively transferred (151). Conversely, there is evidence that a Th2 response may not be required for protection. Specifically, IL-4 and IL-5 knockout C57BL/6 mice were successfully protected from *H. pylori* infection following immunization (76). In addition, studies with IL-4 receptor α-chain-deficient BALB/c mice (which lack both IL-4 and IL-13 signaling) suggested that IL-4 and IL-13 are not required for a protective immune response (129). Whether IFN-γ-producing Th1 cells are required for protective immunity is not yet completely clear (75, 199). However, immunization studies using IL-12 and IL-18 knockout mice indicate that these two Th1 cytokines are required for effective protection against *H. pylori* and suggest that the establishment of an active Th1-type response is required for protection (2, 4, 75). In summary, the role of Th1-type versus Th2-type immune responses in protective immunity to *H. pylori* infection remains incompletely understood. Differences in the mouse strain backgrounds used in various studies potentially complicate interpretation of the data.

There is evidence that protective immunity against *H. pylori* in prophylactically immunized mice may require mast cells. In contrast to immunized wild-type mice, immunized mast cell-deficient mice (W/W v mice) were not protected from challenge with *H. felis* (238). Reconstitution of W/W v mice with bone marrow-derived mast cells restored the ability of W/W v mice to develop a protective immune response following prophylactic vaccination (238). The mechanism by which the mast cells contribute to protective immunity is undefined, but it may be hypothesized that mast cells modulate the activity of T cells or neutrophils through secretion of cytokines or that mast cells have antibacterial activity via the production of nitric oxide or antimicrobial peptides.

Further insight into protective immunity against *H. pylori* can be gleaned by analyzing levels of *H. pylori* colonization (bacterial load or bacterial density) in persistently infected knockout mouse models. The levels of *H. pylori* colonization in SCID mice are significantly higher than those in wild-type mice (61). Conversely, the levels of *H. pylori* colonization in IL-10 knockout mice are about 100-fold lower than those in wild-type mice (43), and in some cases, *H. pylori* is completely eradicated from IL-10 knockout mice (104). Control of *H. pylori* proliferation in IL-10 knockout mice is associated with development of a gastric mucosal inflammatory response that is more severe than that in infected wild-type mice. Therefore, it may be hypothesized that protective immune responses leading to eradication of *H. pylori* are associated with relatively severe gastric mucosal inflammatory responses.

INTERACTIONS BETWEEN *H. PYLORI* AND IMMUNE CELLS IN VITRO

As described in the previous sections of this review, *H. pylori* stimulates a gastric mucosal inflammatory response and resists clearance by host immune defenses. To investigate the molecular mechanisms underlying these phenomena, interactions between *H. pylori* and various types of immune cells have been analyzed in vitro. Because *H. pylori* lives in the gastric mucus layer and does not typically breach the gastric epithelial barrier, contact between *H. pylori* and phagocytic cells may be fairly limited in vivo. Nevertheless, several publications have described ingestion of *H. pylori* by phagocytic cells in human gastric tissue (10, 97, 119, 173). Interactions between *H. pylori* and phagocytic cells probably occur when there are disruptions in the gastric epithelial barrier or in the setting of gastric mucosal injury. Interactions between *H. pylori* and intraepithelial T cells potentially occur commonly even in the absence of gastric epithelial disruptions.

Immune Recognition of *H. pylori* by Gastric Epithelial Cells

Toll-like receptors recognize conserved microbial components, termed "pathogen-associated molecular patterns," and play an important role in initiating innate immune responses to bacterial pathogens. At least 13 different TLRs have been described, 10 of which are expressed in humans. Among the TLRs that recognize gram-negative bacteria, some of the most extensively characterized include TLR2 (which recognizes lipoproteins), TLR4 (gram-negative LPS), TLR5 (flagellin), and TLR9 (bacterial CpG DNA motifs) (223). *H. pylori* adheres to human gastric epithelial cells, and therefore TLRs on gastric epithelial cells would be expected to recognize *H. pylori* PAMPs in vivo. Gastric epithelial cells in the antrum and the corpus of the human stomach are reported to express TLR4, TLR5, and TLR9 (201). In *H. pylori*-negative patients, TLR4, TLR5, and TLR9 are expressed at both the apical and basolateral poles of gastric epithelial cells. In contrast, in *H. pylori*-positive patients, TLR5 and TLR9 are expressed exclusively at the basolateral pole, and TLR4 is expressed at both poles (201). Localization of TLRs to the basolateral poles of epithelial cells would make it unlikely for adherent *H. pylori* to be recognized by these receptors. Cultured primary human gastric cells express TLR2 and TLR5 but not TLR4 (21).

Several studies have sought to characterize the interactions of *H. pylori* PAMPs with TLRs in vitro. These studies have used many different cell types, including primary gastric epithelial cells, gastric epithelial cell lines, and cell lines transfected with plasmids that express TLRs and/or TLR accessory proteins. It is possible that some of the gastric epithelial cell lines used in these experiments do not express certain TLR accessory proteins such as CD14 and MD-2, which are required for TLR4 signaling. Different sources of *H. pylori* PAMPs have been used, including intact bacteria, purified LPS, and flagellin. Because of the many variations in experimental design, the results of these studies have not been uniform. Nevertheless, several general conclusions can be drawn from these studies.

Analyses of the interactions of purified *H. pylori* LPS with TLRs suggest that, in contrast to LPSs from most other gram-negative bacteria, *H. pylori* LPS is not well recognized by TLR4 (21, 103, 206). One study provided evidence that *H. pylori* LPS may act as an antagonist for TLR4 (124). *H. pylori* LPS induced NF-κB activation in HEK293 cells that expressed TLR2 but not in HEK293 cells that expressed TLR4 (206). These data
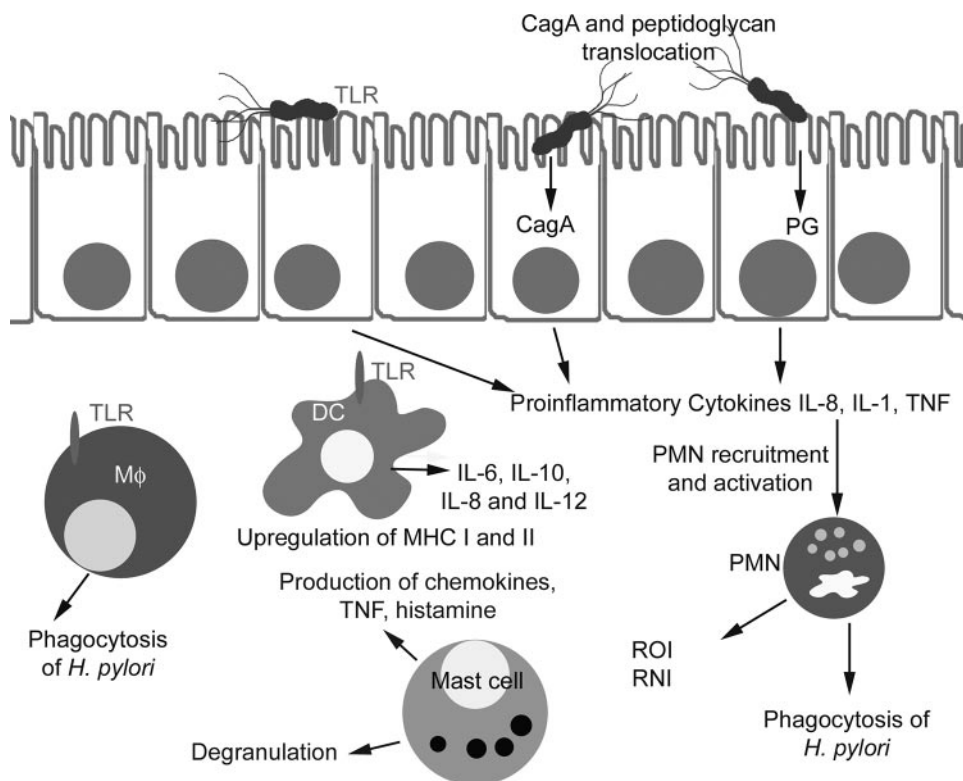
FIG. 3. Innate immune recognition of *H. pylori*. Innate immune recognition of *H. pylori* leads to production of proinflammatory cytokines by macrophages (Mφ), DCs, mast cells, and gastric epithelial cells. Innate immune recognition of *H. pylori* is mediated at least in part through TLRs. In addition, *H. pylori* peptidoglycan (PG) can be recognized by intracellular Nod receptors (239). Interactions between *H. pylori* and gastric epithelial cells lead to activation of NF-κB and alteration in gene transcription in the epithelial cells. Production of IL-8 by epithelial cells leads to recruitment of neutrophils (polymorphonuclear leukocytes [PMNs]), which can phagocytose opsonized bacteria and produce reactive oxygen species (ROI) or reactive nitrogen species (RNI). The activation of mast cells results in degranulation and production of proinflammatory cytokines and chemokines.

suggest that *H. pylori* LPS may be recognized by TLR2 instead of by TLR4. *H. pylori* Hsp60 also is reported to be recognized by TLR2 (224).

Unlike flagellins from gram-negative organisms such as *Salmonella enterica* serovar Typhimurium, *H. pylori* flagellin is not recognized by TLR5 (12, 79, 123). This evasion of TLR5 recognition is attributable to alterations in *H. pylori* FlaA amino acid sequences in the TLR5 recognition site. If the corresponding amino acids are mutated in FlaA from *Salmonella*, the resulting *Salmonella* mutant strain is not recognized by TLR5 (12). Thus, *H. pylori* expresses at least two PAMPs (LPS and flagellin) that are recognized relatively poorly by TLRs and that may not trigger a strong innate immune response.

Recognition of intact *H. pylori* organisms by cultured epithelial cells appears to be dependent on TLR2 and TLR5 and to be independent of TLR4 (136, 141, 206). In one study, dominant negative forms of TLR2, TLR4, and TLR5 were expressed in the human gastric cancer cell line MKN45, and the cells then were incubated with *H. pylori* (206). The expression of chemokines (MIP3α, IL-8, and GROα) in these cells in response to *H. pylori* was dependent on TLR2 and TLR5 signaling but not on TLR4 signaling. These studies suggest that intact *H. pylori* organisms can be recognized by TLR5, despite poor recognition of *H. pylori* flagellin by TLR5. Potentially *H. pylori* components other than flagellin are recognized by TLR5,

or perhaps the results are influenced by variations in the methodology used in different studies.

In addition to recognition of *H. pylori* PAMPs by TLRs, *H. pylori* peptidoglycan can be recognized by Nod1 (CARD4), an intracellular pathogen recognition molecule (239). There is evidence that the type IV secretion system encoded by the *H. pylori* cag PAI delivers *H. pylori* peptidoglycan into epithelial cells. Intracellular recognition of *H. pylori* peptidoglycan by Nod1 leads to activation of NF-κB and altered gene transcription in host cells (239). Compared to gastric epithelial cells from wild-type mice, gastric epithelial cells from Nod1-deficient mice produced significantly less macrophage inflammatory protein-2 in response to *H. pylori* (239).

In summary, *H. pylori* can be recognized in vitro by TLRs as well as the Nod1 receptor, and such recognition probably contributes to initiation of an innate immune response in vivo (Fig. 3). There is no evidence that *H. pylori* can evade detection by TLRs, but certain *H. pylori* PAMPs, such as LPS and flagellin, seem to be poorly recognized by TLRs. This may represent a mechanism by which *H. pylori* down-regulates the intensity of the innate immune response.

It should be noted that the interactions of *H. pylori* with gastric epithelial cells are dependent on characteristics of the *H. pylori* strain. *H. pylori* strains possessing certain adhesins bind to gastric epithelial cells more efficiently than do strains

that lack these adhesins (102). Strains that possess the *cag* PAI stimulate epithelial cells to produce relatively high levels of proinflammatory cytokines compared to strains that lack the *cag* PAI (5, 38, 71, 87, 125, 161, 205, 239). In addition, strains possessing the *cag* PAI and expressing a functionally active form of VacA can cause structural alterations in gastric epithelial cells (46, 95). Both CagA and VacA have been implicated in increasing the permeability of gastric epithelial monolayers (11, 176). A consequence may be entry of *H. pylori* antigens into the lamina propria, which would be expected to trigger an inflammatory response.

Interactions of *H. pylori* with Neutrophils

Neutrophils are recruited when *H. pylori* initially colonizes the human stomach (85, 191), and the gastric mucosal inflammatory response that occurs in the setting of persistent *H. pylori* infection is characterized by infiltration of neutrophils (194, 246). Several specific *H. pylori* factors are known to interact with neutrophils and modulate their function.

H. pylori produces a 150-kDa oligomeric protein known as neutrophil-activating protein (HP-NAP), which is chemotactic for neutrophils and activates neutrophils in vitro (68). HP-NAP stimulates neutrophils to produce reactive oxygen intermediates, and in response to HP-NAP, neutrophils release Ca^{2+} and phosphorylate cytosolic cellular signaling molecules (197). In addition, HP-NAP induces expression of β_2-integrins on the surface of neutrophils (197).

An *H. pylori* outer membrane protein, SabA, also has an important role in human neutrophil activation (235). Wild-type strains of *H. pylori* expressing SabA activate neutrophils, whereas mutant and wild-type strains lacking SabA do not (235). There is evidence that binding of *H. pylori* to neutrophils through SabA-mediated adhesion may stimulate a G-protein-linked signaling pathway and downstream activation of phosphatidylinositol 3-kinase (235).

Whether *H. pylori* can resist phagocytosis by neutrophils is not yet completely resolved (7, 170), but one study reported that uptake of unopsonized *H. pylori* by neutrophils was inefficient compared to uptake of latex-coated beads and that *H. pylori* could inhibit phagocytosis of latex-coated beads or *Neisseria gonorrhoeae* (189). If nonopsonized *H. pylori* organisms are phagocytosed by neutrophils, the bacteria are able to resist intracellular killing (7, 227). One mechanism by which nonopsonized *H. pylori* evades intracellular killing may involve disruption of NADPH oxidase targeting, such that superoxide anions generated in the oxidative burst do not accumulate in the phagosome but instead are released into the extracellular space (7). A catalase-dependent pathway also may have a role in allowing nonopsonized *H. pylori* to evade intracellular killing (189).

The migration of neutrophils in response to chemokines IL-8 and Groα is mediated through the chemokine receptors CXCR1 and CXCR2 (163). *H. pylori* can down-regulate the expression of CXCR1 and CXCR2 in human neutrophils in vitro, and this is predicted to have an inhibitory effect on neutrophil migration (202). In summary, multiple *H. pylori* factors can activate neutrophils, and there is also evidence that *H. pylori* can interfere with the proper functioning of neutrophils.

Interactions of *H. pylori* with Mast Cells

In vitro experiments indicate that whole *H. pylori* bacteria (250) and various *H. pylori* components can activate mast cells. One *H. pylori* factor that can activate mast cells is VacA. VacA can induce mast cell chemotaxis and can stimulate mast cell expression of multiple proinflammatory cytokines, including IL-1, TNF, IL-6, IL-13, and IL-10 (49, 220). VacA induces degranulation of the mast cell line RBL-2H3 but does not induce degranulation of murine bone marrow-derived mast cells (49, 220). HP-NAP also can activate mast cells, resulting in β-hexosaminidase release and IL-6 production (156). Activation of mast cells by *H. pylori* may contribute to the inflammatory response associated with *H. pylori* infection.

Interactions of *H. pylori* with Macrophages

Contact between macrophages and intact *H. pylori* bacteria or *H. pylori* components results in macrophage activation and the secretion of numerous cytokines and chemokines (81, 93, 140). Macrophages recognize *H. pylori* LPS via TLR4 (35, 136) and can also be activated by *H. pylori* proteins, including urease and Hsp60 (81, 93). Macrophage recognition of intact *H. pylori* can be mediated by TLR2 or TLR4 (141, 216).

Although not all studies have reached identical conclusions (170), at least one study reported that *H. pylori* is able to inhibit its own uptake by macrophages (190). When nonopsonized *H. pylori* organisms are internalized by macrophages, they initially localize in phagosomes, which then coalesce into "megasomes" that contain multiple bacteria (8, 193). Ingested *H. pylori* cells have at least some ability to resist intracellular killing (8). One study reported that phagolysosomal fusion is impaired in *H. pylori*-infected macrophages through retention of the tryptophan aspartate-containing coat protein on phagosomes, a phenomenon that is expected to result in increased intracellular survival of the bacteria (258).

Phagocytosis of bacteria by macrophages typically results in localization of the microorganisms within phagosomes that contain protein kinase C (PKC) isoform α (39). PKC activation plays a role in the respiratory burst and phagosome-lysosome fusion (120). Upon phagocytosis of nonopsonized *H. pylori* by macrophages, PKC isoforms ζ and ε accumulate on the forming phagosomes, but the conventional PKC isoform α does not (6). Experiments using specific PKC inhibitors suggest that PKC ζ regulates actin rearrangement and *H. pylori* engulfment (6) and that phagocytosis of nonopsonized *H. pylori* by macrophages may occur via a novel PKC ζ-regulated pathway. The ability of nonopsonized *H. pylori* to resist macrophage killing may be attributable to features of this PKC ζ-mediated phagocytic process. Opsonized *H. pylori* is phagocytosed by a PKC ζ-independent process, which is likely to involve conventional pathways (6).

One mechanism by which *H. pylori* impairs the antimicrobial activity of macrophages involves expression of catalase. In comparison to a wild-type catalase-positive *H. pylori* strain, an isogenic, catalase-deficient strain was more susceptible to macrophage-mediated killing (23). Another mechanism by which *H. pylori* resists macrophage killing is by blocking the production of nitric oxide. This effect is mediated by *H. pylori* arginase, which competes with nitric oxide synthase for arginine

(83). In addition to resisting killing by macrophages, in vitro experiments indicate that *H. pylori* can induce macrophage apoptosis (41, 44, 82). *H. pylori*-induced apoptosis of macrophages may result in impaired innate and adaptive immune responses.

Interactions of *H. pylori* with Dendritic Cells

In response to *H. pylori*, monocyte-derived human DCs express costimulatory molecules and major histocompatibility complex class II proteins (92, 115), which results in increased efficiency of antigen presentation. *H. pylori* also stimulates dendritic cell expression of multiple cytokines, including IL-6, IL-8, IL-10, and IL-12 (88, 115, 240). Similar to several other bacterial pathogens, *H. pylori* can bind to DC-specific ICAM-3-grabbing nonintegrin (DC-SIGN), a DC-specific lectin (15, 27). The expression of cytokines by DCs in response to *H. pylori* is modulated by interactions between *H. pylori* LPS Le antigens (Le^x, Le^y, Le^a, or Le^b) and DC-SIGN (27). Dendritic cells incubated with Le antigen-negative *H. pylori* strains express more IL-6 and less IL-10 than do dendritic cells incubated with Le antigen-positive *H. pylori* (27). Given that IL-10 is known to down-regulate inflammatory responses, the interactions between *H. pylori* LPS Le antigens and DC-SIGN may contribute to suppression of inflammation.

Interactions of *H. pylori* with B Lymphocytes

H. pylori is reported to have several inhibitory effects on B lymphocytes (152, 234). In one study, *H. pylori* VacA interfered with the prelysosomal processing of tetanus toxin in Epstein-Barr virus-transformed B cells, and the ability of these cells to stimulate human CD4$^+$ T cells was impaired in the presence of VacA (152). VacA inhibited the Ii-dependent pathway of antigen presentation mediated by newly synthesized MHC class II molecules but did not affect the pathway dependent on recycling MHC class II (152). Expression of CagA in B cells is reported to inhibit interleukin-3-dependent B-cell proliferation by inhibiting JAK-STAT signaling, which may result in inefficient antibody production and reduced cytokine expression (234).

Interactions of *H. pylori* with T Lymphocytes

In vitro experiments indicate that live *H. pylori* or *H. pylori* products can interfere with multiple functions of T lymphocytes (37, 77, 78, 219, 256) (Fig. 4). One report indicated that *H. pylori* can have proapoptotic effects on T cells (242), but most of the observed effects occur in the absence of cell death. Coincubation of *H. pylori* with T cells results in diminished expression of IL-2 and IL-2 receptor (CD25), inhibition of activation-induced proliferation, and cell cycle arrest (37, 77, 78, 219, 256).

The effects of *H. pylori* on T cells are mediated by several different bacterial factors, one of which is VacA. VacA interferes with the activity of nuclear factor of activated T cells (NFAT), a transcription factor that regulates immune response genes, in Jurkat T cells, resulting in inhibition of IL-2 expression and G$_1$/S cell cycle arrest (37, 77). The effects of VacA on Jurkat cells may be mediated by blocking
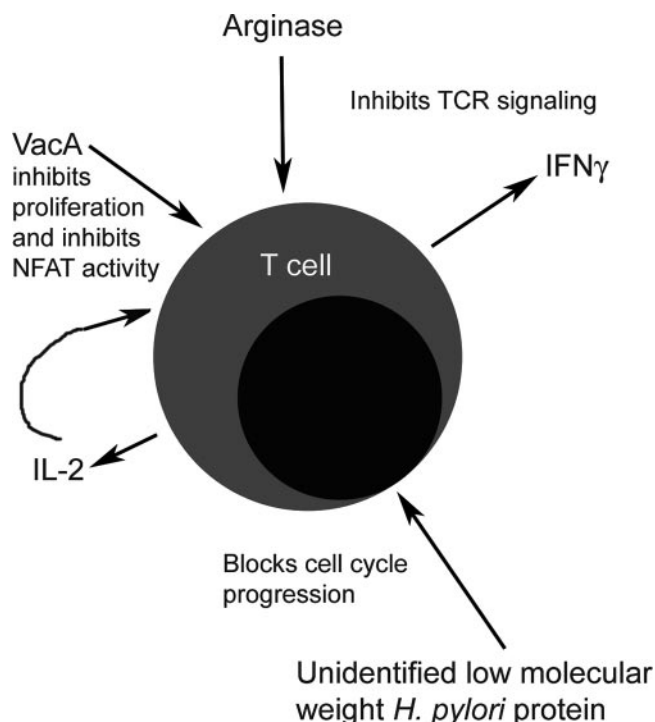

FIG. 4. Effects of *H. pylori* on T lymphocytes. Multiple *H. pylori* factors can suppress T-cell activity. VacA inhibits NFAT activity in T cells, leading to diminished IL-2 production, and also inhibits T-cell proliferation (37, 77, 219). Arginase inhibits T-cell receptor (TCR) signaling (256). An unidentified low-molecular-weight protein has been reported to inhibit T-cell proliferation by blocking cell cycle progression (78).

calcium influx, thereby interfering with the activity of the calcium-dependent phosphatase calcineurin, which is required for NFAT activation (37, 77). VacA also activates intracellular signaling in T cells through mitogen-activated protein kinases MKK3/6 and p38 and the Rac-specific nucleotide exchange factor Vav, thereby causing disorganized actin polymerization (37). Studies of VacA effects on primary human CD4$^+$ T cells indicate that VacA can also inhibit T-cell proliferation through a process that is not dependent on inhibition of NFAT (219).

H. pylori arginase also contributes to inhibition of T-cell proliferation. One study reported that incubation of T cells with a wild-type *H. pylori* strain, but not an arginase mutant strain, caused decreased expression of the CD3ζ chain of the T-cell receptor (256). In addition to VacA and arginase, an uncharacterized low-molecular-weight protein of *H. pylori* has been reported to inhibit proliferation of T lymphocytes (78). This low-molecular-weight *H. pylori* factor is reported to block cell cycle progression at the G$_1$ phase.

CONCLUDING REMARKS

H. pylori persistently colonizes the human stomach despite development of a humoral and cellular immune response. Animal models have been very useful in identifying *H. pylori* factors that are required for colonization of the stomach and for elucidating the roles of various host factors in the devel-

opment of gastric mucosal inflammation. A protective immune response to *H. pylori* can be elicited in animal models by immunization, but the immune effector components that mediate protection remain incompletely defined. *H. pylori* can alter the function of many different types of immune cells in vitro. These in vitro experiments provide important insights into the molecular mechanisms by which *H. pylori* resists immune clearance. However, further studies are needed to determine which in vitro interactions are most relevant in vivo. Future studies, directed toward understanding interactions between *H. pylori* and immune cells in vivo, are expected to lead to important new insights into the mechanisms of *H. pylori* persistence and also may lead to the development of novel therapeutic approaches for eradication of *H. pylori*.

ACKNOWLEDGMENTS

REFERENCES

1. **Akhiani, A. A.** 2005. The role of type-specific antibodies in colonization and infection by *Helicobacter pylori*. Curr. Opin. Infect. Dis. **18:**223–227.
2. **Akhiani, A. A., J. Pappo, Z. Kabok, K. Schon, W. Gao, L. E. Franzen, and N. Lycke.** 2002. Protection against *Helicobacter pylori* infection following immunization is IL-12-dependent and mediated by Th1 cells. J. Immunol. **169:**6977–6984.
3. **Akhiani, A. A., K. Schon, L. E. Franzen, J. Pappo, and N. Lycke.** 2004. *Helicobacter pylori*-specific antibodies impair the development of gastritis, facilitate bacterial colonization, and counteract resistance against infection. J. Immunol. **172:**5024–5033.
4. **Akhiani, A. A., K. Schon, and N. Lycke.** 2004. Vaccine-induced immunity against *Helicobacter pylori* infection is impaired in IL-18-deficient mice. J. Immunol. **173:**3348–3356.
5. **Akopyants, N. S., S. W. Clifton, D. Kersulyte, J. E. Crabtree, B. E. Youree, C. A. Reece, N. O. Bukanov, E. S. Drazek, B. A. Roe, and D. E. Berg.** 1998. Analyses of the cag pathogenicity island of *Helicobacter pylori*. Mol. Microbiol. **28:**37–53.
6. **Allen, L. A., and J. A. Allgood.** 2002. Atypical protein kinase C-zeta is essential for delayed phagocytosis of *Helicobacter pylori*. Curr. Biol. **12:**1762–1766.
7. **Allen, L. A., B. R. Beecher, J. T. Lynch, O. V. Rohner, and L. M. Wittine.** 2005. *Helicobacter pylori* disrupts NADPH oxidase targeting in human neutrophils to induce extracellular superoxide release. J. Immunol. **174:**3658–3667.
8. **Allen, L. A., L. S. Schlesinger, and B. Kang.** 2000. Virulent strains of *Helicobacter pylori* demonstrate delayed phagocytosis and stimulate homotypic phagosome fusion in macrophages. J. Exp. Med. **191:**115–128.
9. **Amedei, A., M. P. Bergman, B. J. Appelmelk, A. Azzurri, M. Benagiano, C. Tamburini, R. van der Zee, J. L. Telford, C. M. Vandenbroucke-Grauls, M. M. D'Elios, and G. Del Prete.** 2003. Molecular mimicry between *Helicobacter pylori* antigens and H+,K+-adenosine triphosphatase in human gastric autoimmunity. J. Exp. Med. **198:**1147–1156.
10. **Amieva, M. R., N. R. Salama, L. S. Tompkins, and S. Falkow.** 2002. *Helicobacter pylori* enter and survive within multivesicular vacuoles of epithelial cells. Cell. Microbiol. **4:**677–690.
11. **Amieva, M. R., R. Vogelmann, A. Covacci, L. S. Tompkins, W. J. Nelson, and S. Falkow.** 2003. Disruption of the epithelial apical-junctional complex by *Helicobacter pylori* CagA. Science **300:**1430–1434.
12. **Andersen-Nissen, E., K. D. Smith, K. L. Strobe, S. L. Barrett, B. T. Cookson, S. M. Logan, and A. Aderem.** 2005. Evasion of Toll-like receptor 5 by flagellated bacteria. Proc. Natl. Acad. Sci. USA **102:**9247–9252.
13. **Appelmelk, B. J., Y. Q. An, M. Geerts, B. G. Thijs, H. A. de Boer, D. M. MacLaren, J. de Graaff, and J. H. Nuijens.** 1994. Lactoferrin is a lipid A-binding protein. Infect. Immun. **62:**2628–2632.
14. **Appelmelk, B. J., S. L. Martin, M. A. Monteiro, C. A. Clayton, A. A. McColm, P. Zheng, T. Verboom, J. J. Maaskant, D. H. van den Eijnden, C. H. Hokke, M. B. Perry, C. M. Vandenbroucke-Grauls, and J. G. Kusters.** 1999. Phase variation in *Helicobacter pylori* lipopolysaccharide due to changes in the lengths of poly(C) tracts in α3-fucosyltransferase genes. Infect. Immun. **67:**5361–5366.

15. **Appelmelk, B. J., I. van Die, S. J. van Vliet, C. M. Vandenbroucke-Grauls, T. B. Geijtenbeek, and Y. van Kooyk.** 2003. Cutting edge: carbohydrate profiling identifies new pathogens that interact with dendritic cell-specific ICAM-3-grabbing nonintegrin on dendritic cells. J. Immunol. **170:**1635–1639.
16. **Aras, R. A., W. Fischer, G. I. Perez-Perez, M. Crosatti, T. Ando, R. Haas, and M. J. Blaser.** 2003. Plasticity of repetitive DNA sequences within a bacterial (type IV) secretion system component. J. Exp. Med. **198:**1349–1360.
17. **Archimandritis, A., S. Sougioultzis, P. G. Foukas, M. Tzivras, P. Davaris, and H. M. Moutsopoulos.** 2000. Expression of HLA-DR, costimulatory molecules B7-1, B7-2, intercellular adhesion molecule-1 (ICAM-1) and Fas ligand (FasL) on gastric epithelial cells in Helicobacter pylori gastritis; influence of *H. pylori* eradication. Clin. Exp. Immunol. **119:**464–471.
18. **Asahi, M., T. Azuma, S. Ito, Y. Ito, H. Suto, Y. Nagai, M. Tsubokawa, Y. Tohyama, S. Maeda, M. Omata, T. Suzuki, and C. Sasakawa.** 2000. *Helicobacter pylori* CagA protein can be tyrosine phosphorylated in gastric epithelial cells. J. Exp. Med. **191:**593–602.
19. **Aspinall, G. O., and M. A. Monteiro.** 1996. Lipopolysaccharides of *Helicobacter pylori* strains P466 and MO19: structures of the O antigen and core oligosaccharide regions. Biochemistry **35:**2498–2504.
20. **Ayraud, S., B. Janvier, and J. L. Fauchere.** 2002. Experimental colonization of mice by fresh clinical isolates of *Helicobacter pylori* is not influenced by the cagA status and the vacA genotype. FEMS Immunol. Med. Microbiol. **34:**169–172.
21. **Backhed, F., B. Rokbi, E. Torstensson, Y. Zhao, C. Nilsson, D. Seguin, S. Normark, A. M. Buchan, and A. Richter-Dahlfors.** 2003. Gastric mucosal recognition of *Helicobacter pylori* is independent of Toll-like receptor 4. J. Infect. Dis. **187:**829–836.
22. **Bamford, K. B., X. Fan, S. E. Crowe, J. F. Leary, W. K. Gourley, G. K. Luthra, E. G. Brooks, D. Y. Graham, V. E. Reyes, and P. B. Ernst.** 1998. Lymphocytes in the human gastric mucosa during *Helicobacter pylori* infection have a T helper cell 1 phenotype. Gastroenterology **114:**482–492.
23. **Basu, M., S. J. Czinn, and T. G. Blanchard.** 2004. Absence of catalase reduces long-term survival of *Helicobacter pylori* in macrophage phagosomes. Helicobacter **9:**211–216.
24. **Bauer, F., K. Schweimer, E. Kluver, J. R. Conejo-Garcia, W. G. Forssmann, P. Rosch, K. Adermann, and H. Sticht.** 2001. Structure determination of human and murine beta-defensins reveals structural conservation in the absence of significant sequence similarity. Protein Sci. **10:**2470–2479.
25. **Beales, I., J. Calam, L. Post, S. Srinivasan, T. Yamada, and J. DelValle.** 1997. Effect of transforming growth factor alpha and interleukin 8 on somatostatin release from canine fundic D cells. Gastroenterology **112:**136–143.
26. **Berg, D. J., N. A. Lynch, R. G. Lynch, and D. M. Lauricella.** 1998. Rapid development of severe hyperplastic gastritis with gastric epithelial dedifferentiation in *Helicobacter felis*-infected IL-10(−/−) mice. Am. J. Pathol. **152:**1377–1386.
27. **Bergman, M. P., A. Engering, H. H. Smits, S. J. van Vliet, A. A. van Bodegraven, H. P. Wirth, M. L. Kapsenberg, C. M. J. E. Vanderbroucke-Grauls, Y. van Kooyk, and B. J. Appelmelk.** 2004. *Helicobacter pylori* modulates the T helper cell 1/T helper cell 2 balance through phase-variable interaction between lipopolysaccharide and DC-SIGN. J. Exp. Med. **200:**979–990.
28. **Berstad, A. E., M. Kilian, K. N. Valnes, and P. Brandtzaeg.** 1999. Increased mucosal production of monomeric IgA1 but no IgA1 protease activity in *Helicobacter pylori* gastritis. Am. J. Pathol. **155:**1097–1104.
29. **Betten, A., J. Bylund, T. Cristophe, F. Boulay, A. Romero, K. Hellstrand, and C. Dahlgren.** 2001. A proinflammatory peptide from *Helicobacter pylori* activates monocytes to induce lymphocyte dysfunction and apoptosis. J. Clin. Investig. **108:**1221–1228.
30. **Blanchard, T. G., S. J. Czinn, R. Maurer, W. D. Thomas, G. Soman, and J. G. Nedrud.** 1995. Urease-specific monoclonal antibodies prevent *Helicobacter felis* infection in mice. Infect. Immun. **63:**1394–1399.
31. **Blanchard, T. G., S. J. Czinn, R. W. Redline, N. Sigmund, G. Harriman, and J. G. Nedrud.** 1999. Antibody-independent protective mucosal immunity to gastric *Helicobacter* infection in mice. Cell. Immunol. **191:**74–80.
32. **Blanchard, T. G., F. Yu, C. L. Hsieh, and R. W. Redline.** 2003. Severe inflammation and reduced bacteria load in murine *Helicobacter* infection caused by lack of phagocyte oxidase activity. J. Infect. Dis. **187:**1609–1615.
33. **Blaser, M. J.** 2005. The biology of cag in the *Helicobacter pylori*-human interaction. Gastroenterology **128:**1512–1515.
34. **Blaser, M. J., and J. C. Atherton.** 2004. *Helicobacter pylori* persistence: biology and disease. J. Clin. Investig. **113:**321–333.
35. **Bliss, C. M., Jr., D. T. Golenbock, S. Keates, J. K. Linevsky, and C. P. Kelly.** 1998. *Helicobacter pylori* lipopolysaccharide binds to CD14 and stimulates release of interleukin-8, epithelial neutrophil-activating peptide 78, and monocyte chemotactic protein 1 by human monocytes. Infect. Immun. **66:**5357–5363.
36. **Bogstedt, A. K., S. Nava, T. Wadstrom, and L. Hammarstrom.** 1996. *Helicobacter pylori* infections in IgA deficiency: lack of role for the secretory immune system. Clin. Exp. Immunol. **105:**202–204.

37. **Boncristiano, M., S. R. Paccani, S. Barone, C. Ulivieri, L. Patrussi, D. Ilver, A. Amedei, M. M. D'Elios, J. L. Telford, and C. T. Baldari.** 2003. The *Helicobacter pylori* vacuolating toxin inhibits T cell activation by two independent mechanisms. J. Exp. Med. **198:**1887–1897.

38. **Brandt, S., T. Kwok, R. Hartig, W. Konig, and S. Backert.** 2005. NF-κB activation and potentiation of proinflammatory responses by the *Helicobacter pylori* CagA protein. Proc. Natl. Acad. Sci. USA **102:**9300–9305.

39. **Breton, A., and A. Descoteaux.** 2000. Protein kinase C-alpha participates in FcγR-mediated phagocytosis in macrophages. Biochem. Biophys. Res. Commun. **276:**472–476.

40. **Censini, S., C. Lange, Z. Xiang, J. E. Crabtree, P. Ghiara, M. Borodovsky, R. Rappuoli, and A. Covacci.** 1996. cag, a pathogenicity island of *Helicobacter pylori*, encodes type I-specific and disease-associated virulence factors. Proc. Natl. Acad. Sci. USA **93:**14648–14653.

41. **Chaturvedi, R., Y. Cheng, M. Asim, F. I. Bussiere, H. Xu, A. P. Gobert, A. Hacker, R. A. Casero, Jr., and K. T. Wilson.** 2004. Induction of polyamine oxidase 1 by *Helicobacter pylori* causes macrophage apoptosis by hydrogen peroxide release and mitochondrial membrane depolarization. J. Biol. Chem. **279:**40161–40173.

42. **Chen, W., D. Shu, and V. S. Chadwick.** 1999. *Helicobacter pylori* infection in interleukin-4-deficient and transgenic mice. Scand. J. Gastroenterol. **34:** 987–992.

43. **Chen, W., D. Shu, and V. S. Chadwick.** 2001. *Helicobacter pylori* infection: mechanism of colonization and functional dyspepsia. Reduced colonization of gastric mucosa by *Helicobacter pylori* in mice deficient in interleukin-10. J. Gastroenterol. Hepatol. **16:**377–383.

44. **Cheng, Y., R. Chaturvedi, M. Asim, F. I. Bussiere, H. Xu, R. A. Casero, Jr., and K. T. Wilson.** 2005. *Helicobacter pylori*-induced macrophage apoptosis requires activation of ornithine decarboxylase by c-Myc. J. Biol. Chem. **280:**22492–22496.

45. **Correa, P.** 1992. Human gastric carcinogenesis: a multistep and multifactorial process. Cancer Res. **52:**6735–6740.

46. **Cover, T. L., and S. R. Blanke.** 2005. *Helicobacter pylori* VacA, a paradigm for toxin multifunctionality. Nat. Rev. Microbiol. **3:**320–332.

47. **Crabtree, J. E., T. M. Shallcross, R. V. Heatley, and J. I. Wyatt.** 1991. Mucosal tumour necrosis factor alpha and interleukin-6 in patients with *Helicobacter pylori* associated gastritis. Gut **32:**1473–1477.

48. **Czinn, S. J., A. Cai, and J. G. Nedrud.** 1993. Protection of germ-free mice from infection by *Helicobacter felis* after active oral or passive IgA immunization. Vaccine **11:**637–642.

49. **de Bernard, M., A. Cappon, L. Pancotto, P. Ruggiero, J. Rivera, G. Del Giudice, and C. Montecucco.** 2005. The *Helicobacter pylori* VacA cytotoxin activates RBL-2H3 cells by inducing cytosolic calcium oscillations. Cell. Microbiol. **7:**191–198.

50. **Del Giudice, G., A. Covacci, J. L. Telford, C. Montecucco, and R. Rappuoli.** 2001. The design of vaccines against *Helicobacter pylori* and their development. Annu. Rev. Immunol. **19:**523–563.

51. **D'Elios, M. M., M. P. Bergman, A. Amedei, B. J. Appelmelk, and G. Del Prete.** 2004. *Helicobacter pylori* and gastric autoimmunity. Microbes Infect. **6:**1395–1401.

52. **D'Elios, M. M., M. Manghetti, M. De Carli, F. Costa, C. T. Baldari, D. Burroni, J. L. Telford, S. Romagnani, and G. Del Prete.** 1997. T helper 1 effector cells specific for *Helicobacter pylori* in the gastric antrum of patients with peptic ulcer disease. J. Immunol. **158:**962–967.

53. **Deml, L., M. Aigner, J. Decker, A. Eckhardt, C. Schutz, P. R. Mittl, S. Barabas, S. Denk, G. Knoll, N. Lehn, and W. Schneider-Brachert.** 2005. Characterization of the *Helicobacter pylori* cysteine-rich protein A as a T-helper cell type 1 polarizing agent. Infect. Immun. **73:**4732–4742.

54. **Di Tommaso, A., Z. Xiang, M. Bugnoli, P. Pileri, N. Figura, P. F. Bayeli, R. Rappuoli, S. Abrignani, and M. T. De Magistris.** 1995. *Helicobacter pylori*-specific CD4$^+$ T-cell clones from peripheral blood and gastric biopsies. Infect. Immun. **63:**1102–1106.

55. **Dixon, M. F., R. M. Genta, J. H. Yardley, and P. Correa.** 1996. Classification and grading of gastritis. The updated Sydney system. Am. J. Surg. Pathol. **20:**1161–1181.

56. **Dooley, C. P., H. Cohen, P. L. Fitzgibbons, M. Bauer, M. D. Appleman, G. I. Perez-Perez, and M. J. Blaser.** 1989. Prevalence of *Helicobacter pylori* infection and histologic gastritis in asymptomatic persons. N. Engl. J. Med. **321:**1562–1566.

57. **Dubois, A., D. E. Berg, E. T. Incecik, N. Fiala, L. M. Heman-Ackah, J. Del Valle, M. Yang, H. P. Wirth, G. I. Perez-Perez, and M. J. Blaser.** 1999. Host specificity of *Helicobacter pylori* strains and host responses in experimentally challenged nonhuman primates. Gastroenterology **116:**90–96.

58. **Dubois, A., N. Fiala, L. M. Heman-Ackah, E. S. Drazek, A. Tarnawski, W. N. Fishbein, G. I. Perez-Perez, and M. J. Blaser.** 1994. Natural gastric infection with *Helicobacter pylori* in monkeys: a model for spiral bacteria infection in humans. Gastroenterology **106:**1405–1417.

59. **Eaton, K. A., and S. Krakowka.** 1994. Effect of gastric pH on urease-dependent colonization of gnotobiotic piglets by *Helicobacter pylori*. Infect. Immun. **62:**3604–3607.

60. **Eaton, K. A., M. Mefford, and T. Thevenot.** 2001. The role of T cell subsets

61. **Eaton, K. A., S. R. Ringler, and S. J. Danon.** 1999. Murine splenocytes induce severe gastritis and delayed-type hypersensitivity and suppress bacterial colonization in *Helicobacter pylori*-infected SCID mice. Infect. Immun. **67:**4594–4602.

62. **Eaton, K. A., S. Suerbaum, C. Josenhans, and S. Krakowka.** 1996. Colonization of gnotobiotic piglets by *Helicobacter pylori* deficient in two flagellin genes. Infect. Immun. **64:**2445–2448.

63. **El-Omar, E. M.** 2001. The importance of interleukin 1beta in *Helicobacter pylori* associated disease. Gut **48:**743–747.

64. **El-Omar, E. M., M. Carrington, W. H. Chow, K. E. McColl, J. H. Bream, H. A. Young, J. Herrera, J. Lissowska, C. C. Yuan, N. Rothman, G. Lanyon, M. Martin, J. F. Fraumeni, Jr., and C. S. Rabkin.** 2000. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. Nature **404:**398–402.

65. **El-Omar, E. M., M. Carrington, W. H. Chow, K. E. McColl, J. H. Bream, H. A. Young, J. Herrera, J. Lissowska, C. C. Yuan, N. Rothman, G. Lanyon, M. Martin, J. F. Fraumeni, Jr., and C. S. Rabkin.** 2001. The role of interleukin-1 polymorphisms in the pathogenesis of gastric cancer. Nature **412:**99.

66. **El-Omar, E. M., C. S. Rabkin, M. D. Gammon, T. L. Vaughan, H. A. Risch, J. B. Schoenberg, J. L. Stanford, S. T. Mayne, J. Goedert, W. J. Blot, J. F. Fraumeni, Jr., and W. H. Chow.** 2003. Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. Gastroenterology **124:**1193–1201.

67. **Ermak, T. H., P. J. Giannasca, R. Nichols, G. A. Myers, J. Nedrud, R. Weltzin, C. K. Lee, H. Kleanthous, and T. P. Monath.** 1998. Immunization of mice with urease vaccine affords protection against *Helicobacter pylori* infection in the absence of antibodies and is mediated by MHC class II-restricted responses. J. Exp. Med. **188:**2277–2288.

68. **Evans, D. J., Jr., D. G. Evans, T. Takemura, H. Nakano, H. C. Lampert, D. Y. Graham, D. N. Granger, and P. R. Kvietys.** 1995. Characterization of a *Helicobacter pylori* neutrophil-activating protein. Infect. Immun. **63:**2213–2220.

69. **Ferrero, R. L., J. M. Thiberge, and A. Labigne.** 1997. Local immunoglobulin G antibodies in the stomach may contribute to immunity against *Helicobacter* infection in mice. Gastroenterology **113:**185–194.

70. **Figueiredo, C., J. C. Machado, P. Pharoah, R. Seruca, S. Sousa, R. Carvalho, A. F. Capelinha, W. Quint, C. Caldas, L. J. van Doorn, F. Carneiro, and M. Sobrinho-Simoes.** 2002. *Helicobacter pylori* and interleukin 1 genotyping: an opportunity to identify high-risk individuals for gastric carcinoma. J. Natl. Cancer Inst. **94:**1680–1687.

71. **Fischer, W., J. Puls, R. Buhrdorf, B. Gebert, S. Odenbreit, and R. Haas.** 2001. Systematic mutagenesis of the *Helicobacter pylori* cag pathogenicity island: essential genes for CagA translocation in host cells and induction of interleukin-8. Mol. Microbiol. **42:**1337–1348.

72. **Fox, J. G., P. Beck, C. A. Dangler, M. T. Whary, T. C. Wang, H. N. Shi, and C. Nagler-Anderson.** 2000. Concurrent enteric helminth infection modulates inflammation and gastric immune responses and reduces *Helicobacter*-induced gastric atrophy. Nat. Med. **6:**536–542.

73. **Franco, A. T., D. A. Israel, M. K. Washington, U. Krishna, J. G. Fox, A. B. Rogers, A. S. Neish, L. Collier-Hyams, G. I. Perez-Perez, M. Hatakeyama, R. Whitehead, K. Gaus, D. P. O'Brien, J. Romero-Gallo, and R. M. Peek, Jr.** 2005. Activation of beta-catenin by carcinogenic *Helicobacter pylori*. Proc. Natl. Acad. Sci. USA **102:**10646–10651.

74. **Frye, M., J. Bargon, B. Lembcke, T. O. Wagner, and R. Gropp.** 2000. Differential expression of human alpha- and beta-defensins mRNA in gastrointestinal epithelia. Eur. J. Clin. Investig. **30:**695–701.

75. **Garhart, C. A., F. P. Heinzel, S. J. Czinn, and J. G. Nedrud.** 2003. Vaccine-induced reduction of *Helicobacter pylori* colonization in mice is interleukin-12 dependent but gamma interferon and inducible nitric oxide synthase independent. Infect. Immun. **71:**910–921.

76. **Garhart, C. A., J. G. Nedrud, F. P. Heinzel, N. E. Sigmund, and S. J. Czinn.** 2003. Vaccine-induced protection against *Helicobacter pylori* in mice lacking both antibodies and interleukin-4. Infect. Immun. **71:**3628–3633.

77. **Gebert, B., W. Fischer, E. Weiss, R. Hoffmann, and R. Haas.** 2003. *Helicobacter pylori* vacuolating cytotoxin inhibits T lymphocyte activation. Science **301:**1099–1102.

78. **Gerhard, M., C. Schmees, P. Voland, N. Endres, M. Sander, W. Reindl, R. Rad, M. Oelsner, T. Decker, M. Mempel, L. Hengst, and C. Prinz.** 2005. A secreted low-molecular-weight protein from *Helicobacter pylori* induces cell-cycle arrest of T cells. Gastroenterology **128:**1327–1339.

79. **Gewirtz, A. T., Y. Yu, U. S. Krishna, D. A. Israel, S. L. Lyons, and R. M. Peek, Jr.** 2004. *Helicobacter pylori* flagellin evades Toll-like receptor 5-mediated innate immunity. J. Infect. Dis. **189:**1914–1920.

80. **Gifford, J. L., H. N. Hunter, and H. J. Vogel.** 2005. Lactoferricin: a lactoferrin-derived peptide with antimicrobial, antiviral, antitumor and immunological properties. Cell. Mol. Life Sci. **62:**2588–2598.

81. **Gobert, A. P., J. C. Bambou, C. Werts, V. Balloy, M. Chignard, A. P. Moran, and R. L. Ferrero.** 2004. *Helicobacter pylori* heat shock protein 60 mediates interleukin-6 production by macrophages via a Toll-like receptor (TLR)-2-,

and cytokines in the pathogenesis of *Helicobacter pylori* gastritis in mice. J. Immunol. **166:**7456–7461.

TLR-4-, and myeloid differentiation factor 88-independent mechanism. J. Biol. Chem. **279:**245–250.

82. **Gobert, A. P., Y. Cheng, J. Y. Wang, J. L. Boucher, R. K. Iyer, S. D. Cederbaum, R. A. Casero, Jr., J. C. Newton, and K. T. Wilson.** 2002. *Helicobacter pylori* induces macrophage apoptosis by activation of arginase II. J. Immunol. **168:**4692–4700.

83. **Gobert, A. P., D. J. McGee, M. Akhtar, G. L. Mendz, J. C. Newton, Y. Cheng, H. L. Mobley, and K. T. Wilson.** 2001. *Helicobacter pylori* arginase inhibits nitric oxide production by eukaryotic cells: a strategy for bacterial survival. Proc. Natl. Acad. Sci. USA **98:**13844–13849.

84. **Gottwein, J. M., T. G. Blanchard, O. S. Targoni, J. C. Eisenberg, B. M. Zagorski, R. W. Redline, J. G. Nedrud, M. Tary-Lehmann, P. V. Lehmann, and S. J. Czinn.** 2001. Protective anti-*Helicobacter* immunity is induced with aluminum hydroxide or complete Freund's adjuvant by systemic immunization. J Infect. Dis. **184:**308–314.

85. **Graham, D. Y., L. C. Alpert, J. L. Smith, and H. H. Yoshimura.** 1988. Iatrogenic *Campylobacter pylori* infection is a cause of epidemic achlorhydria. Am. J. Gastroenterol. **83:**974–980.

86. **Graham, D. Y., A. R. Opekun, M. S. Osata, H. M. T. El-Zimaity, C. K. Lee, Y. Yamaoka, W. A. Qureshi, M. Cadoz, and T. P. Monath.** 2004. Challenge model for *Helicobacter pylori* infection in human volunteers. Gut **53:**1235–1243.

87. **Guillemin, K., N. R. Salama, L. S. Tompkins, and S. Falkow.** 2002. Cag pathogenicity island-specific responses of gastric epithelial cells to *Helicobacter pylori* infection. Proc. Natl. Acad. Sci. USA **99:**15136–15141.

88. **Guiney, D. G., P. Hasegawa, and S. P. Cole.** 2003. *Helicobacter pylori* preferentially induces interleukin 12 (IL-12) rather than IL-6 or IL-10 in human dendritic cells. Infect. Immun. **71:**4163–4166.

89. **Guo, B. P., and J. J. Mekalanos.** 2002. Rapid genetic analysis of *Helicobacter pylori* gastric mucosal colonization in suckling mice. Proc. Natl. Acad. Sci. USA **99:**8354–8359.

90. **Guruge, J. L., P. G. Falk, R. G. Lorenz, M. Dans, H. P. Wirth, M. J. Blaser, D. E. Berg, and J. I. Gordon.** 1998. Epithelial attachment alters the outcome of *Helicobacter pylori* infection. Proc. Natl. Acad. Sci. USA **95:**3925–3930.

91. **Haeberle, H. A., M. Kubin, K. B. Bamford, R. Garofalo, D. Y. Graham, F. El-Zaatari, R. Karttunen, S. E. Crowe, V. E. Reyes, and P. B. Ernst.** 1997. Differential stimulation of interleukin-12 (IL-12) and IL-10 by live and killed *Helicobacter pylori* in vitro and association of IL-12 production with gamma interferon-producing T cells in the human gastric mucosa. Infect. Immun. **65:**4229–4235.

92. **Hafsi, N., P. Voland, S. Schwendy, R. Rad, W. Reindl, M. Gerhard, and C. Prinz.** 2004. Human dendritic cells respond to *Helicobacter pylori*, promoting NK cell and Th1-effector responses in vitro. J. Immunol. **173:**1249–1257.

93. **Harris, P. R., P. B. Ernst, S. Kawabata, H. Kiyono, M. F. Graham, and P. D. Smith.** 1998. Recombinant *Helicobacter pylori* urease activates primary mucosal macrophages. J. Infect. Dis. **178:**1516–1520.

94. **Hase, K., M. Murakami, M. Iimura, S. P. Cole, Y. Horibe, T. Ohtake, M. Obonyo, R. L. Gallo, L. Eckmann, and M. F. Kagnoff.** 2003. Expression of LL-37 by human gastric epithelial cells as a potential host defense mechanism against *Helicobacter pylori*. Gastroenterology **125:**1613–1625.

95. **Hatakeyama, M.** 2004. Oncogenic mechanisms of the *Helicobacter pylori* CagA protein. Nat. Rev. Cancer **4:**688–694.

96. **Hayashi, S., T. Sugiyama, K. Yokota, H. Isogai, E. Isogai, K. Oguma, M. Asaka, N. Fujii, and Y. Hirai.** 1998. Analysis of immunoglobulin A antibodies to *Helicobacter pylori* in serum and gastric juice in relation to mucosal inflammation. Clin. Diagn. Lab. Immunol. **5:**617–621.

97. **Hazell, S. L., A. Lee, L. Brady, and W. Hennessy.** 1986. *Campylobacter pyloridis* and gastritis: association with intercellular spaces and adaptation to an environment of mucus as important factors in colonization of the gastric epithelium. J. Infect. Dis. **153:**658–663.

98. **Higashi, H., R. Tsutsumi, S. Muto, T. Sugiyama, T. Azuma, M. Asaka, and M. Hatakeyama.** 2002. SHP-2 tyrosine phosphatase as an intracellular target of *Helicobacter pylori* CagA protein. Science **295:**683–686.

99. **Hoffman, P. S., N. Vats, D. Hutchison, J. Butler, K. Chisholm, G. Sisson, A. Raudonikiene, J. S. Marshall, and S. J. Veldhuyzen van Zanten.** 2003. Development of an interleukin-12-deficient mouse model that is permissive for colonization by a motile KE26695 strain of *Helicobacter pylori*. Infect. Immun. **71:**2534–2541.

100. **Honda, S., T. Fujioka, M. Tokieda, R. Satoh, A. Nishizono, and M. Nasu.** 1998. Development of *Helicobacter pylori*-induced gastric carcinoma in Mongolian gerbils. Cancer Res. **58:**4255–4259.

101. **Hwang, I. R., T. Kodama, S. Kikuchi, K. Sakai, L. E. Peterson, D. Y. Graham, and Y. Yamaoka.** 2002. Effect of interleukin 1 polymorphisms on gastric mucosal interleukin 1β production in *Helicobacter pylori* infection. Gastroenterology **123:**1793–1803.

102. **Ilver, D., A. Arnqvist, J. Ogren, I. M. Frick, D. Kersulyte, E. T. Incecik, D. E. Berg, A. Covacci, L. Engstrand, and T. Boren.** 1998. *Helicobacter pylori* adhesin binding fucosylated histo-blood group antigens revealed by retagging. Science **279:**373–377.

103. **Ishihara, S., M. A. Rumi, Y. Kadowaki, C. F. Ortega-Cava, T. Yuki, N. Yoshino, Y. Miyaoka, H. Kazumori, N. Ishimura, Y. Amano, and Y.**

104. **Kinoshita.** 2004. Essential role of MD-2 in TLR4-dependent signaling during *Helicobacter pylori*-associated gastritis. J. Immunol. **173:**1406–1416.

104. **Ismail, H. F., P. Fick, J. Zhang, R. G. Lynch, and D. J. Berg.** 2003. Depletion of neutrophils in IL-10(−/−) mice delays clearance of gastric *Helicobacter* infection and decreases the Th1 immune response to *Helicobacter*. J. Immunol. **170:**3782–3789.

105. **Israel, D. A., N. Salama, C. N. Arnold, S. F. Moss, T. Ando, H. P. Wirth, K. T. Tham, M. Camorlinga, M. J. Blaser, S. Falkow, and R. M. Peek, Jr.** 2001. *Helicobacter pylori* strain-specific differences in genetic content, identified by microarray, influence host inflammatory responses. J. Clin. Investig. **107:**611–620.

106. **Jeremy, A. H., Y. Du, M. F. Dixon, P. A. Robinson, and J. E. Crabtree.** 2006. Protection against *Helicobacter pylori* infection in the Mongolian gerbil after prophylactic vaccination. Microbes Infect. **8:**340–346.

107. **Jones, N. L., A. S. Day, H. Jennings, P. T. Shannon, E. Galindo-Mata, and P. M. Sherman.** 2002. Enhanced disease severity in *Helicobacter pylori*-infected mice deficient in Fas signaling. Infect. Immun. **70:**2591–2597.

108. **Jonsson, K., B. P. Guo, H. J. Monstein, J. J. Mekalanos, and G. Kronvall.** 2004. Molecular cloning and characterization of two *Helicobacter pylori* genes coding for plasminogen-binding proteins. Proc. Natl. Acad. Sci. USA **101:**1852–1857.

109. **Kamradt, A. E., M. Greiner, P. Ghiara, and S. H. Kaufmann.** 2000. *Helicobacter pylori* infection in wild-type and cytokine-deficient C57BL/6 and BALB/c mouse mutants. Microb. Infect. **2:**593–597.

110. **Karttunen, R., T. Karttunen, H. P. Ekre, and T. T. MacDonald.** 1995. Interferon gamma and interleukin 4 secreting cells in the gastric antrum in *Helicobacter pylori* positive and negative gastritis. Gut **36:**341–345.

111. **Kavermann, H., B. P. Burns, K. Angermuller, S. Odenbreit, W. Fischer, K. Melchers, and R. Haas.** 2003. Identification and characterization of *Helicobacter pylori* genes essential for gastric colonization. J. Exp. Med. **197:**813–822.

112. **Kawakubo, M., Y. Ito, Y. Okimura, M. Kobayashi, K. Sukara, S. Kasama, M. N. Fukuda, M. Fukuda, T. Katsuyama, and J. Nakayama.** 2004. Natural antibiotic function of a human gastric mucin against *Helicobacter pylori* infection. Science **305:**1003–1006.

113. **Kelso, A., A. B. Troutt, E. Maraskovsky, N. M. Gough, L. Morris, M. H. Pech, and J. A. Thomson.** 1991. Heterogeneity in lymphokine profiles of CD4+ and CD8+ T cells and clones activated in vivo and in vitro. Immunol. Rev. **123:**85–114.

114. **Khamri, W., A. P. Moran, M. L. Worku, Q. N. Karim, M. M. Walker, H. Annuk, J. A. Ferris, B. J. Appelmelk, P. Eggleton, K. B. Reid, and M. R. Thursz.** 2005. Variations in *Helicobacter pylori* lipopolysaccharide to evade the innate immune component surfactant protein D. Infect. Immun. **73:**7677–7686.

115. **Kranzer, K., A. Eckhardt, M. Aigner, G. Knoll, L. Deml, C. Speth, N. Lehn, M. Rehli, and W. Schneider-Brachert.** 2004. Induction of maturation and cytokine release of human dendritic cells by *Helicobacter pylori*. Infect. Immun. **72:**4416–4423.

116. **Kuipers, E. J., D. A. Israel, J. G. Kusters, M. M. Gerrits, J. Weel, A. van Der Endeqq, R. W. van Der Hulstqq, H. P. Wirth, J. Hook-Nikanne, S. A. Thompson, and M. J. Blaser.** 2000. Quasispecies development of *Helicobacter pylori* observed in paired isolates obtained years apart from the same host. J. Infect. Dis. **181:**273–282.

117. **Kuipers, E. J., G. I. Perez-Perez, S. G. Meuwissen, and M. J. Blaser.** 1995. *Helicobacter pylori* and atrophic gastritis: importance of the cagA status. J. Natl. Cancer Inst. **87:**1777–1780.

118. **Kumar, V.** 2004. Homeostatic control of immunity by TCR peptide-specific Tregs. J. Clin. Investig. **114:**1222–1226.

119. **Kwok, T., S. Backert, H. Schwarz, J. Berger, and T. F. Meyer.** 2002. Specific entry of *Helicobacter pylori* into cultured gastric epithelial cells via a zipperlike mechanism. Infect. Immun. **70:**2108–2120.

120. **Larsen, E. C., J. A. DiGennaro, N. Saito, S. Mehta, D. J. Loegering, J. E. Mazurkiewicz, and M. R. Lennartz.** 2000. Differential requirement for classic and novel PKC isoforms in respiratory burst and phagocytosis in RAW 264.7 cells. J. Immunol. **165:**2809–2817.

121. **Lee, A.** 2000. Animal models of gastroduodenal ulcer disease. Baillieres Best Pract. Res. Clin. Gastroenterol. **14:**75–96.

122. **Lee, C. K., R. Weltzin, W. D. Thomas, Jr., H. Kleanthous, T. H. Ermak, G. Soman, J. E. Hill, S. K. Ackerman, and T. P. Monath.** 1995. Oral immunization with recombinant *Helicobacter pylori* urease induces secretory IgA antibodies and protects mice from challenge with *Helicobacter felis*. J. Infect. Dis. **172:**161–172.

123. **Lee, S. K., A. Stack, E. Katzowitsch, S. I. Aizawa, S. Suerbaum, and C. Josenhans.** 2003. *Helicobacter pylori* flagellins have very low intrinsic activity to stimulate human gastric epithelial cells via TLR5. Microbes Infect. **5:**1345–1356.

124. **Lepper, P. M., M. Triantafilou, C. Schumann, E. M. Schneider, and K. Triantafilou.** 2005. Lipopolysaccharides from *Helicobacter pylori* can act as antagonists for Toll-like receptor 4. Cell. Microbiol. **7:**519–528.

125. **Li, S. D., D. Kersulyte, I. J. Lindley, B. Neelam, D. E. Berg, and J. E. Crabtree.** 1999. Multiple genes in the left half of the *cag* pathogenicity island of *Helicobacter pylori* are required for tyrosine kinase-dependent

transcription of interleukin-8 in gastric epithelial cells. Infect. Immun. **67:** 3893–3899.

126. Lindholm, C., M. Quiding-Jarbrink, H. Lonroth, A. Hamlet, and A. M. Svennerholm. 1998. Local cytokine response in *Helicobacter pylori*-infected subjects. Infect. Immun. **66:**5964–5971.

127. Loughlin, M. F., F. M. Barnard, D. Jenkins, G. J. Sharples, and P. J. Jenks. 2003. *Helicobacter pylori* mutants defective in RuvC Holliday junction resolvase display reduced macrophage survival and spontaneous clearance from the murine gastric mucosa. Infect. Immun. **71:**2022–2031.

128. Lu, H., P. I. Hsu, D. Y. Graham, and Y. Yamaoka. 2005. Duodenal ulcer promoting gene of *Helicobacter pylori*. Gastroenterology **128:**833–848.

129. Lucas, B., D. Bumann, A. Walduck, J. Koesling, L. Develioglu, T. F. Meyer, and T. Aebischer. 2001. Adoptive transfer of CD4$^+$ T cells specific for subunit A of *Helicobacter pylori* urease reduces *H. pylori* stomach colonization in mice in the absence of interleukin-4 (IL-4)/IL-13 receptor signaling. Infect. Immun. **69:**1714–1721.

130. Lundgren, A., E. Stromberg, A. Sjoling, C. Lindholm, K. Enarsson, A. Edebo, E. Johnsson, E. Suri-Payer, P. Larsson, A. Rudin, A. M. Svennerholm, and B. S. Lundin. 2005. Mucosal FOXP3-expressing CD4$^+$ CD25^{high} regulatory T cells in *Helicobacter pylori*-infected patients. Infect. Immun. **73:**523–531.

131. Lundgren, A., E. Suri-Payer, K. Enarsson, A. M. Svennerholm, and B. S. Lundin. 2003. *Helicobacter pylori*-specific CD4$^+$ CD25^{high} regulatory T cells suppress memory T-cell responses to *H. pylori* in infected individuals. Infect. Immun. **71:**1755–1762.

132. Lundgren, A., C. Trollmo, A. Edebo, A. M. Svennerholm, and B. S. Lundin. 2005. *Helicobacter pylori*-specific CD4$^+$ T cells home to and accumulate in the human *Helicobacter pylori*-infected gastric mucosa. Infect. Immun. **73:** 5612–5619.

133. Luqmani, Y. A., T. A. Campbell, C. Bennett, R. C. Coombes, and I. M. Paterson. 1991. Expression of lactoferrin in human stomach. Int. J. Cancer **49:**684–687.

134. Machado, J. C., C. Figueiredo, P. Canedo, P. Pharoah, R. Carvalho, S. Nabais, C. Castro Alves, M. L. Campos, L. J. Van Doorn, C. Caldas, R. Seruca, F. Carneiro, and M. Sobrinho-Simoes. 2003. A proinflammatory genetic profile increases the risk for chronic atrophic gastritis and gastric carcinoma. Gastroenterology **125:**364–371.

135. Machado, J. C., P. Pharoah, S. Sousa, R. Carvalho, C. Oliveira, C. Figueiredo, A. Amorim, R. Seruca, C. Caldas, F. Carneiro, and M. Sobrinho-Simoes. 2001. Interleukin 1B and interleukin 1RN polymorphisms are associated with increased risk of gastric carcinoma. Gastroenterology **121:**823–829.

136. Maeda, S., M. Akanuma, Y. Mitsuno, Y. Hirata, K. Ogura, H. Yoshida, Y. Shiratori, and M. Omata. 2001. Distinct mechanism of *Helicobacter pylori*-mediated NF-kappa B activation between gastric cancer cells and monocytic cells. J. Biol. Chem. **276:**44856–44864.

137. Mahdavi, J., B. Sonden, M. Hurtig, F. O. Olfat, L. Forsberg, N. Roche, J. Angstrom, T. Larsson, S. Teneberg, K. A. Karlsson, S. Altraja, T. Wadstrom, D. Kersulyte, D. E. Berg, A. Dubois, C. Petersson, K. E. Magnusson, T. Norberg, F. Lindh, B. B. Lundskog, A. Arnqvist, L. Hammarstrom, and T. Boren. 2002. *Helicobacter pylori* SabA adhesin in persistent infection and chronic inflammation. Science **297:**573–578.

138. Mahler, M., C. Janke, S. Wagner, and H. J. Hedrich. 2002. Differential susceptibility of inbred mouse strains to *Helicobacter pylori* infection. Scand. J. Gastroenterol. **37:**267–278.

139. Mai, U. E., G. I. Perez-Perez, J. B. Allen, S. M. Wahl, M. J. Blaser, and P. D. Smith. 1992. Surface proteins from *Helicobacter pylori* exhibit chemotactic activity for human leukocytes and are present in gastric mucosa. J. Exp. Med. **175:**517–525.

140. Mai, U. E., G. I. Perez-Perez, L. M. Wahl, S. M. Wahl, M. J. Blaser, and P. D. Smith. 1991. Soluble surface proteins from *Helicobacter pylori* activate monocytes/macrophages by lipopolysaccharide-independent mechanism. J. Clin. Investig. **87:**894–900.

141. Mandell, L., A. P. Moran, A. Cocchiarella, J. Houghton, N. Taylor, J. G. Fox, T. C. Wang, and E. A. Kurt-Jones. 2004. Intact gram-negative *Helicobacter pylori*, *Helicobacter felis*, and *Helicobacter hepaticus* bacteria activate innate immunity via Toll-like receptor 2 but not Toll-like receptor 4. Infect. Immun. **72:**6446–6454.

142. Marchetti, M., B. Arico, D. Burroni, N. Figura, R. Rappuoli, and P. Ghiara. 1995. Development of a mouse model of *Helicobacter pylori* infection that mimics human disease. Science **267:**1655–1658.

143. Marshall, B. J., J. A. Armstrong, D. B. McGechie, and R. J. Glancy. 1985. Attempt to fulfil Koch's postulates for pyloric *Campylobacter*. Med. J. Aust. **142:**436–439.

144. Marshall, B. J., L. J. Barrett, C. Prakash, R. W. McCallum, and R. L. Guerrant. 1990. Urea protects *Helicobacter (Campylobacter) pylori* from the bactericidal effect of acid. Gastroenterology **99:**697–702.

145. Marshall, B. J., and J. R. Warren. 1984. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet **i:**1311–1315.

146. Mattsson, A., H. Lonroth, M. Quiding-Jarbrink, and A. M. Svennerholm. 1998. Induction of B cell responses in the stomach of *Helicobacter pylori*-infected subjects after oral cholera vaccination. J. Clin. Investig. **102:**51–56.

147. Mattsson, A., M. Quiding-Jarbrink, H. Lonroth, A. Hamlet, I. Ahlstedt, and A. Svennerholm. 1998. Antibody-secreting cells in the stomachs of symptomatic and asymptomatic *Helicobacter pylori*-infected subjects. Infect. Immun. **66:**2705–2712.

148. Matz-Rensing, K., E. Kunz, C. Kraft, D. Lorenzen, S. Suerbaum, and F. J. Kaup. 2001. Experimental *Helicobacter pylori* infection of rhesus macaques (Macaca mulatta). Int. J. Med. Microbiol. **291:**33–43.

149. McGee, D. J., M. L. Langford, E. L. Watson, J. E. Carter, Y. T. Chen, and K. M. Ottemann. 2005. Colonization and inflammation deficiencies in Mongolian gerbils infected by *Helicobacter pylori* chemotaxis mutants. Infect. Immun. **73:**1820–1827.

150. Minoura, T., S. Kato, S. Otsu, M. Kodama, T. Fujioka, K. Iinuma, and A. Nishizono. 2005. Influence of age and duration of infection on bacterial load and immune responses to *Helicobacter pylori* infection in a murine model. Clin. Exp. Immunol. **139:**43–47.

151. Mohammadi, M., J. Nedrud, R. Redline, N. Lycke, and S. J. Czinn. 1997. Murine CD4 T-cell response to *Helicobacter* infection: TH1 cells enhance gastritis and TH2 cells reduce bacterial load. Gastroenterology **113:**1848–1857.

152. Molinari, M., M. Salio, C. Galli, N. Norais, R. Rappuoli, A. Lanzavecchia, and C. Montecucco. 1998. Selective inhibition of Ii-dependent antigen presentation by *Helicobacter pylori* toxin VacA. J. Exp. Med. **187:**135–140.

153. Montecucco, C., and R. Rappuoli. 2001. Living dangerously: how *Helicobacter pylori* survives in the human stomach. Nat. Rev. Mol. Cell Biol. **2:**457–466.

154. Monteiro, M. A., K. H. Chan, D. A. Rasko, D. E. Taylor, P. Y. Zheng, B. J. Appelmelk, H. P. Wirth, M. Yang, M. J. Blaser, S. O. Hynes, A. P. Moran, and M. B. Perry. 1998. Simultaneous expression of type 1 and type 2 Lewis blood group antigens by *Helicobacter pylori* lipopolysaccharides. J. Biol. Chem. **273:**11533–11543.

155. Montemurro, P., G. Barbuti, W. G. Dundon, G. Del Giudice, R. Rappuoli, M. Colucci, P. De Rinaldis, C. Montecucco, N. Semeraro, and E. Papini. 2001. *Helicobacter pylori* neutrophil-activating protein stimulates tissue factor and plasminogen activator inhibitor-2 production by human blood mononuclear cells. J. Infect. Dis. **183:**1055–1062.

156. Montemurro, P., H. Nishioka, W. G. Dundon, M. de Bernard, G. Del Giudice, R. Rappuoli, and C. Montecucco. 2002. The neutrophil-activating protein (HP-NAP) of *Helicobacter pylori* is a potent stimulant of mast cells. Eur. J. Immunol. **32:**671–676.

157. Moran, A. P., and G. O. Aspinall. 1998. Unique structural and biological features of *Helicobacter pylori* lipopolysaccharides. Prog. Clin. Biol. Res. **397:**37–49.

158. Moran, A. P., W. Khamri, M. M. Walker, and M. R. Thursz. 2005. Role of surfactant protein D (SP-D) in innate immunity in the gastric mucosa: evidence of interaction with *Helicobacter pylori* lipopolysaccharide. J. Endotoxin Res. **11:**357–362.

159. Morris, A., and G. Nicholson. 1987. Ingestion of *Campylobacter pyloridis* causes gastritis and raised fasting gastric pH. Am. J. Gastroenterol. **82:**192–199.

160. Morris, A. J., M. R. Ali, G. I. Nicholson, et al. 1991. Long-term follow up of voluntary ingestion of *Helicobacter pylori*. Ann. Intern. Med. **114:**662–663.

161. Mueller, A., D. S. Merrell, J. Grimm, and S. Falkow. 2004. Profiling of microdissected gastric epithelial cells reveals a cell type-specific response to *Helicobacter pylori* infection. Gastroenterology **127:**1446–1462.

162. Muotiala, A., I. M. Helander, L. Pyhala, T. U. Kosunen, and A. P. Moran. 1992. Low biological activity of *Helicobacter pylori* lipopolysaccharide. Infect. Immun. **60:**1714–1716.

163. Murphy, P. M. 1997. Neutrophil receptors for interleukin-8 and related CXC chemokines. Semin. Hematol. **34:**311–318.

164. Murray, E., W. Khamri, M. M. Walker, P. Eggleton, A. P. Moran, J. A. Ferris, S. Knapp, Q. N. Karim, M. Worku, P. Strong, K. B. Reid, and M. R. Thursz. 2002. Expression of surfactant protein D in the human gastric mucosa and during *Helicobacter pylori* infection. Infect. Immun. **70:**1481–1487.

165. Neutra, M. R., E. Pringault, and J. P. Kraehenbuhl. 1996. Antigen sampling across epithelial barriers and induction of mucosal immune responses. Annu. Rev. Immunol. **14:**275–300.

166. Nilsson, C., A. Sillen, L. Eriksson, M. L. Strand, H. Enroth, S. Normark, P. Falk, and L. Engstrand. 2003. Correlation between *cag* pathogenicity island composition and *Helicobacter pylori*-associated gastroduodenal disease. Infect. Immun. **71:**6573–6581.

167. Nishi, T., K. Okazaki, K. Kawasaki, T. Fukui, H. Tamaki, M. Matsuura, M. Asada, T. Watanabe, K. Uchida, N. Watanabe, H. Nakase, M. Ohana, H. Hiai, and T. Chiba. 2003. Involvement of myeloid dendritic cells in the development of gastric secondary lymphoid follicles in *Helicobacter pylori*-infected neonatally thymectomized BALB/c mice. Infect. Immun. **71:**2153–2162.

168. Nurgalieva, Z. Z., M. E. Conner, A. R. Opekun, C. Q. Zheng, S. N. Elliott, P. B. Ernst, M. Osato, M. K. Estes, and D. Y. Graham. 2005. B-cell and T-cell immune responses to experimental *Helicobacter pylori* infection in humans. Infect. Immun. **73:**2999–3006.

169. Obonyo, M., D. G. Guiney, J. Harwood, J. Fierer, and S. P. Cole. 2002. Role

of gamma interferon in *Helicobacter pylori* induction of inflammatory mediators during murine infection. Infect. Immun. **70:**3295–3299.

170. **Odenbreit, S., B. Gebert, J. Puls, W. Fischer, and R. Haas.** 2001. Interaction of *Helicobacter pylori* with professional phagocytes: role of the cag pathogenicity island and translocation, phosphorylation and processing of CagA. Cell. Microbiol. **3:**21–31.

171. **Odenbreit, S., J. Puls, B. Sedlmaier, E. Gerland, W. Fischer, and R. Haas.** 2000. Translocation of *Helicobacter pylori* CagA into gastric epithelial cells by type IV secretion. Science **287:**1497–1500.

172. **Ogura, K., S. Maeda, M. Nakao, T. Watanabe, M. Tada, T. Kyutoku, H. Yoshida, Y. Shiratori, and M. Omata.** 2000. Virulence factors of *Helicobacter pylori* responsible for gastric diseases in Mongolian gerbil. J. Exp. Med. **192:**1601–1610.

173. **Oh, J. D., S. M. Karam, and J. I. Gordon.** 2005. Intracellular *Helicobacter pylori* in gastric epithelial progenitors. Proc. Natl. Acad. Sci. USA **102:**5186–5191.

174. **O'Rourke, J. L., and A. Lee.** 2003. Animal models of *Helicobacter pylori* infection and disease. Microbes Infect. **5:**741–748.

175. **Orsi, N.** 2004. The antimicrobial activity of lactoferrin: current status and perspectives. Biometals **17:**189–196.

176. **Papini, E., B. Satin, N. Norais, M. de Bernard, J. L. Telford, R. Rappuoli, and C. Montecucco.** 1998. Selective increase of the permeability of polarized epithelial cell monolayers by *Helicobacter pylori* vacuolating toxin. J. Clin. Investig. **102:**813–820.

177. **Pappo, J., D. Torrey, L. Castriotta, A. Savinainen, Z. Kabok, and A. Ibraghimov.** 1999. *Helicobacter pylori* infection in immunized mice lacking major histocompatibility complex class I and class II functions. Infect. Immun. **67:**337–341.

178. **Parsonnet, J.** 1998. Helicobacter pylori. Infect. Dis. Clin. N. Am. **12:**185–197.

179. **Peek, R. M., Jr., and M. J. Blaser.** 2002. *Helicobacter pylori* and gastrointestinal tract adenocarcinomas. Nat. Rev. Cancer **2:**28–37.

180. **Perez-Perez, G. I., B. M. Dworkin, J. E. Chodos, and M. J. Blaser.** 1988. *Campylobacter pylori* antibodies in humans. Ann. Intern. Med. **109:**11–17.

181. **Perez-Perez, G. I., V. L. Shepherd, J. D. Morrow, and M. J. Blaser.** 1995. Activation of human THP-1 cells and rat bone marrow-derived macrophages by *Helicobacter pylori* lipopolysaccharide. Infect. Immun. **63:**1183–1187.

182. **Peterson, R. A., II, T. Hoepf, and K. A. Eaton.** 2003. Adoptive transfer of splenocytes in SCID mice implicates CD4+ T cells in apoptosis and epithelial proliferation associated with *Helicobacter pylori*-induced gastritis. Comp. Med. **53:**498–509.

183. **Peterson, W. L.** 1991. *Helicobacter pylori* and peptic ulcer disease. N. Engl. J. Med. **324:**1043–1048.

184. **Quiding-Jarbrink, M., B. S. Lundin, H. Lonroth, and A. M. Svennerholm.** 2001. CD4+ and CD8+ T cell responses in *Helicobacter pylori*-infected individuals. Clin. Exp. Immunol. **123:**81–87.

185. **Quigley, E. M., and L. A. Turnberg.** 1987. pH of the microclimate lining human gastric and duodenal mucosa in vivo. Studies in control subjects and in duodenal ulcer patients. Gastroenterology **92:**1876–1884.

186. **Rad, R., M. Gerhard, R. Lang, M. Schoniger, T. Rosch, W. Schepp, I. Becker, H. Wagner, and C. Prinz.** 2002. The *Helicobacter pylori* blood group antigen-binding adhesin facilitates bacterial colonization and augments a nonspecific immune response. J. Immunol. **168:**3033–3041.

187. **Rad, R., C. Prinz, B. Neu, M. Neuhofer, M. Zeitner, P. Voland, I. Becker, W. Schepp, and M. Gerhard.** 2003. Synergistic effect of *Helicobacter pylori* virulence factors and interleukin-1 polymorphisms for the development of severe histological changes in the gastric mucosa. J. Infect. Dis. **188:**272–281.

188. **Raghavan, S., M. Fredriksson, A. M. Svennerholm, J. Holmgren, and E. Suri-Payer.** 2003. Absence of CD4+CD25+ regulatory T cells is associated with a loss of regulation leading to increased pathology in *Helicobacter pylori*-infected mice. Clin. Exp. Immunol. **132:**393–400.

189. **Ramarao, N., S. D. Gray-Owen, and T. F. Meyer.** 2000. *Helicobacter pylori* induces but survives the extracellular release of oxygen radicals from professional phagocytes using its catalase activity. Mol. Microbiol. **38:**103–113.

190. **Ramarao, N., and T. F. Meyer.** 2001. *Helicobacter pylori* resists phagocytosis by macrophages: quantitative assessment by confocal microscopy and fluorescence-activated cell sorting. Infect. Immun. **69:**2604–2611.

191. **Ramsey, E. J., K. V. Carey, W. L. Peterson, J. J. Jackson, F. K. Murphy, N. W. Read, K. B. Taylor, J. S. Trier, and J. S. Fordtran.** 1979. Epidemic gastritis with hypochlorhydria. Gastroenterology **76:**1449–1457.

192. **Rieder, G., J. L. Merchant, and R. Haas.** 2005. *Helicobacter pylori* cag-type IV secretion system facilitates corpus colonization to induce precancerous conditions in Mongolian gerbils. Gastroenterology **128:**1229–1242.

193. **Rittig, M. G., B. Shaw, D. P. Letley, R. J. Thomas, R. H. Argent, and J. C. Atherton.** 2003. *Helicobacter pylori*-induced homotypic phagosome fusion in human monocytes is independent of the bacterial vacA and cag status. Cell. Microbiol. **5:**887–899.

194. **Rocha, G. A., D. M. Queiroz, E. N. Mendes, A. J. Barbosa, G. F. Lima Junior, and C. A. Oliveira.** 1991. *Helicobacter pylori* acute gastritis: histo-

logical, endoscopical, clinical, and therapeutic features. Am. J. Gastroenterol. **86:**1592–1595.

195. **Rossi, G., P. Ruggiero, S. Peppoloni, L. Pancotto, D. Fortuna, L. Lauretti, G. Volpini, S. Mancianti, M. Corazza, E. Taccini, F. Di Pisa, R. Rappuoli, and G. Del Giudice.** 2004. Therapeutic vaccination against *Helicobacter pylori* in the beagle dog experimental model: safety, immunogenicity, and efficacy. Infect. Immun. **72:**3252–3259.

196. **Sakagami, T., M. Dixon, J. O'Rourke, R. Howlett, F. Alderuccio, J. Vella, T. Shimoyama, and A. Lee.** 1996. Atrophic gastric changes in both *Helicobacter felis* and *Helicobacter pylori* infected mice are host dependent and separate from antral gastritis. Gut **39:**639–648.

197. **Satin, B., G. Del Giudice, V. Della Bianca, S. Dusi, C. Laudanna, F. Tonello, D. Kelleher, R. Rappuoli, C. Montecucco, and F. Rossi.** 2000. The neutrophil-activating protein (HP-NAP) of *Helicobacter pylori* is a protective antigen and a major virulence factor. J. Exp. Med. **191:**1467–1476.

198. **Saunders, N. J., J. F. Peden, D. W. Hood, and E. R. Moxon.** 1998. Simple sequence repeats in the *Helicobacter pylori* genome. Mol. Microbiol. **27:**1091–1098.

199. **Sawai, N., M. Kita, T. Kodama, T. Tanahashi, Y. Yamaoka, Y. Tagawa, Y. Iwakura, and J. Imanishi.** 1999. Role of gamma interferon in *Helicobacter pylori*-induced gastric inflammatory responses in a mouse model. Infect. Immun. **67:**279–285.

200. **Schibli, D. J., P. M. Hwang, and H. J. Vogel.** 1999. Structure of the antimicrobial peptide tritrpticin bound to micelles: a distinct membrane-bound peptide fold. Biochemistry **38:**16749–16755.

201. **Schmausser, B., M. Andrulis, S. Endrich, S. K. Lee, C. Josenhans, H. K. Muller-Hermelink, and M. Eck.** 2004. Expression and subcellular distribution of toll-like receptors TLR4, TLR5 and TLR9 on the gastric epithelium in *Helicobacter pylori* infection. Clin. Exp. Immunol. **136:**521–526.

202. **Schmausser, B., C. Josenhans, S. Endrich, S. Suerbaum, C. Sitaru, M. Andrulis, S. Brandlein, P. Rieckmann, H. K. Muller-Hermelink, and M. Eck.** 2004. Downregulation of CXCR1 and CXCR2 expression on human neutrophils by *Helicobacter pylori*: a new pathomechanism in *H. pylori* infection? Infect. Immun. **72:**6773–6779.

203. **Schreiber, S., M. Konradt, C. Groll, P. Scheid, G. Hanauer, H. O. Werling, C. Josenhans, and S. Suerbaum.** 2004. The spatial orientation of *Helicobacter pylori* in the gastric mucus. Proc. Natl. Acad. Sci. USA **101:**5024–5029.

204. **Segal, E. D., J. Cha, J. Lo, S. Falkow, and L. S. Tompkins.** 1999. Altered states: involvement of phosphorylated CagA in the induction of host cellular growth changes by Helicobacter pylori. Proc. Natl. Acad. Sci. USA **96:**14559–14564.

205. **Segal, E. D., C. Lange, A. Covacci, L. S. Tompkins, and S. Falkow.** 1997. Induction of host signal transduction pathways by *Helicobacter pylori*. Proc. Natl. Acad. Sci. USA **94:**7595–7599.

206. **Smith, M. F., Jr., A. Mitchell, G. Li, S. Ding, A. M. Fitzmaurice, K. Ryan, S. Crowe, and J. B. Goldberg.** 2003. Toll-like receptor (TLR) 2 and TLR5, but not TLR4, are required for *Helicobacter pylori*-induced NF-kappa B activation and chemokine expression by epithelial cells. J. Biol. Chem. **278:**32552–32560.

207. **Smythies, L. E., K. B. Waites, J. R. Lindsey, P. R. Harris, P. Ghiara, and P. D. Smith.** 2000. *Helicobacter pylori*-induced mucosal inflammation is Th1 mediated and exacerbated in IL-4, but not IFN-gamma, gene-deficient mice. J. Immunol. **165:**1022–1029.

208. **Sobala, G. M., J. E. Crabtree, M. F. Dixon, C. J. Schorah, J. D. Taylor, B. J. Rathbone, R. V. Heatley, and A. T. Axon.** 1991. Acute *Helicobacter pylori* infection: clinical features, local and systemic immune response, gastric mucosal histology, and gastric juice ascorbic acid concentrations. Gut **32:**1415–1418.

209. **Solnick, J. V., D. R. Canfield, S. Yang, and J. Parsonnet.** 1999. Rhesus monkey (Macaca mulatta) model of *Helicobacter pylori*: noninvasive detection and derivation of specific-pathogen-free monkeys. Lab. Anim. Sci. **49:**197–201.

210. **Solnick, J. V., L. M. Hansen, N. R. Salama, J. K. Boonjakuakul, and M. Syvanen.** 2004. Modification of *Helicobacter pylori* outer membrane protein expression during experimental infection of rhesus macaques. Proc. Natl. Acad. Sci. **101:**2106–2111.

211. **Sommer, F., G. Faller, P. Konturek, T. Kirchner, E. G. Hahn, J. Zeus, M. Rollinghoff, and M. Lohoff.** 1998. Antrum- and corpus mucosa-infiltrating CD4+ lymphocytes in *Helicobacter pylori* gastritis display a Th1 phenotype. Infect. Immun. **66:**5543–5546.

212. **Sommer, F., G. Faller, M. Rollinghoff, T. Kirchner, T. W. Mak, and M. Lohoff.** 2001. Lack of gastritis and of an adaptive immune response in interferon regulatory factor-1-deficient mice infected with *Helicobacter pylori*. Eur. J. Immunol. **31:**396–402.

213. **Soto, G., C. T. Bautista, D. E. Roth, R. H. Gilman, B. Velapatino, M. Ogura, G. Dailide, M. Razuri, R. Meza, U. Katz, T. P. Monath, D. E. Berg, and D. N. Taylor.** 2003. *Helicobacter pylori* reinfection is common in Peruvian adults after antibiotic eradication therapy. J. Infect. Dis. **188:**1263–1275.

214. **Stein, M., R. Rappuoli, and A. Covacci.** 2000. Tyrosine phosphorylation of the *Helicobacter pylori* CagA antigen after cag-driven host cell translocation. Proc. Natl. Acad. Sci. USA **97:**1263–1268.

215. Strober, W., B. Kelsall, I. Fuss, T. Marth, B. Ludviksson, R. Ehrhardt, and M. Neurath. 1997. Reciprocal IFN-gamma and TGF-beta responses regulate the occurrence of mucosal inflammation. Immunol. Today 18:61–64.

216. Su, B., P. J. Ceponis, S. Lebel, H. Huynh, and P. M. Sherman. 2003. *Helicobacter pylori* activates Toll-like receptor 4 expression in gastrointestinal epithelial cells. Infect. Immun. 71:3496–3502.

217. Suerbaum, S., and P. Michetti. 2002. *Helicobacter pylori* infection. N. Engl. J. Med. 347:1175–1186.

218. Sun, X. L., H. M. Baker, S. C. Shewry, G. B. Jameson, and E. N. Baker. 1999. Structure of recombinant human lactoferrin expressed in *Aspergillus awamori*. Acta Crystallogr. D 55:403–407.

219. Sundrud, M. S., V. J. Torres, D. Unutmaz, and T. L. Cover. 2004. Inhibition of primary human T cell proliferation by *Helicobacter pylori* vacuolating toxin (VacA) is independent of VacA effects on IL-2 secretion. Proc. Natl. Acad. Sci. USA 101:7727–7732.

220. Supajatura, V., H. Ushio, A. Wada, K. Yahiro, K. Okumura, H. Ogawa, T. Hirayama, and C. Ra. 2002. Cutting edge: VacA, a vacuolating cytotoxin of *Helicobacter pylori*, directly activates mast cells for migration and production of proinflammatory cytokines. J. Immunol. 168:2603–2607.

221. Sutton, P., J. Wilson, T. Kosaka, I. Wolowczuk, and A. Lee. 2000. Therapeutic immunization against *Helicobacter pylori* infection in the absence of antibodies. Immunol. Cell Biol. 78:28–30.

222. Suzuki, T., K. Kato, S. Ohara, K. Noguchi, H. Sekine, H. Nagura, and T. Shimosegawa. 2002. Localization of antigen-presenting cells in *Helicobacter pylori*-infected gastric mucosa. Pathol. Int. 52:265–271.

223. Takeda, K., and S. Akira. 2003. Toll receptors and pathogen resistance. Cell. Microbiol. 5:143–153.

224. Takenaka, R., K. Yokota, K. Ayada, M. Mizuno, Y. Zhao, Y. Fujinami, S. N. Lin, T. Toyokawa, H. Okada, Y. Shiratori, and K. Oguma. 2004. *Helicobacter pylori* heat-shock protein 60 induces inflammatory responses through the Toll-like receptor-triggered pathway in cultured human gastric epithelial cells. Microbiology 150:3913–3922.

225. Talley, N. J., J. E. Ormand, C. A. Frie, and A. R. Zinsmeister. 1992. Stability of pH gradients in vivo across the stomach in *Helicobacter pylori* gastritis, dyspepsia, and health. Am. J. Gastroenterol. 87:590–594.

226. Taylor, D. N., and M. J. Blaser. 1991. The epidemiology of Helicobacter pylori infection. Epidemiol. Rev. 13:42–59.

227. Teneberg, S., M. Jurstrand, K. A. Karlsson, and D. Danielsson. 2000. Inhibition of nonopsonic *Helicobacter pylori*-induced activation of human neutrophils by sialylated oligosaccharides. Glycobiology 10:1171–1181.

228. Terres, A. M., and J. M. Pajares. 1998. An increased number of follicles containing activated CD69+ helper T cells and proliferating CD71+ B cells are found in *H. pylori*-infected gastric mucosa. Am. J. Gastroenterol. 93:579–583.

229. Thalmaier, U., N. Lehn, K. Pfeffer, M. Stolte, M. Vieth, and W. Schneider-Brachert. 2002. Role of tumor necrosis factor alpha in *Helicobacter pylori* gastritis in tumor necrosis factor receptor 1-deficient mice. Infect. Immun. 70:3149–3155.

230. Tham, K. T., R. M. Peek, Jr., J. C. Atherton, T. L. Cover, G. I. Perez-Perez, Y. Shyr, and M. J. Blaser. 2001. *Helicobacter pylori* genotypes, host factors, and gastric mucosal histopathology in peptic ulcer disease. Hum. Pathol. 32:264–273.

231. Thompson, L. J., S. J. Danon, J. E. Wilson, J. L. O'Rourke, N. R. Salama, S. Falkow, H. Mitchell, and A. Lee. 2004. Chronic *Helicobacter pylori* infection with Sydney strain 1 and a newly identified mouse-adapted strain (Sydney strain 2000) in C57BL/6 and BALB/c mice. Infect. Immun. 72:4668–4679.

232. Togawa, S., T. Joh, M. Itoh, N. Katsuda, H. Ito, K. Matsuo, K. Tajima, and N. Hamajima. 2005. Interleukin-2 gene polymorphisms associated with increased risk of gastric atrophy from *Helicobacter pylori* infection. Helicobacter 10:172–178.

233. Uemura, N., S. Okamoto, S. Yamamoto, N. Matsumura, S. Yamaguchi, M. Yamakido, K. Taniyama, N. Sasaki, and R. J. Schlemper. 2001. *Helicobacter pylori* infection and the development of gastric cancer. N. Engl. J. Med. 345:784–789.

234. Umehara, S., H. Higashi, N. Ohnishi, M. Asaka, and M. Hatakeyama. 2003. Effects of *Helicobacter pylori* CagA protein on the growth and survival of B lymphocytes, the origin of MALT lymphoma. Oncogene 22:8337–8342.

235. Unemo, M., M. Aspholm-Hurtig, D. Ilver, J. Bergstrom, T. Boren, D. Danielsson, and S. Teneberg. 2005. The sialic acid binding SabA adhesin of *Helicobacter pylori* is essential for nonopsonic activation of human neutrophils. J. Biol. Chem. 280:15390–15397.

236. van Doorn, L. J., C. Figueiredo, R. Sanna, A. Plaisier, P. Schneeberger, W. de Boer, and W. Quint. 1998. Clinical relevance of the cagA, vacA, and iceA status of *Helicobacter pylori*. Gastroenterology 115:58–66.

237. van Doorn, N. E., E. P. van Rees, F. Namavar, and J. de Graaff. 1998. Local cellular immune response in the acute phase of gastritis in mice induced chemically and by *Helicobacter pylori*. J. Med. Microbiol. 47:863–870.

238. Velin, D., D. Bachmann, H. Bouzourene, and P. Michetti. 2005. Mast cells are critical mediators of vaccine-induced *Helicobacter* clearance in the mouse model. Gastroenterology 129:142–155.

239. Viala, J., C. Chaput, I. G. Boneca, A. Cardona, S. E. Girardin, A. P. Moran, R. Athman, S. Memet, M. R. Huerre, A. J. Coyle, P. S. DiStefano, P. J. Sansonetti, A. Labigne, J. Bertin, D. J. Philpott, and R. L. Ferrero. 2004. Nod1 responds to peptidoglycan delivered by the *Helicobacter pylori* cag pathogenicity island. Nat. Immunol. 5:1166–1174.

240. Voland, P., N. Hafsi, M. Zeitner, S. Laforsch, H. Wagner, and C. Prinz. 2003. Antigenic properties of HpaA and Omp18, two outer membrane proteins of *Helicobacter pylori*. Infect. Immun. 71:3837–3843.

241. Wang, G., Z. Ge, D. A. Rasko, and D. E. Taylor. 2000. Lewis antigens in Helicobacter pylori: biosynthesis and phase variation. Mol. Microbiol. 36:1187–1196.

242. Wang, J., E. G. Brooks, K. B. Bamford, T. L. Denning, J. Pappo, and P. B. Ernst. 2001. Negative selection of T cells by *Helicobacter pylori* as a model for bacterial strain selection by immune evasion. J. Immunol. 167:926–934.

243. Warren, J. R. 2000. Gastric pathology associated with Helicobacter pylori. Gastroenterol. Clin. N. Am. 29:705–751.

244. Watanabe, T., M. Tada, H. Nagai, S. Sasaki, and M. Nakao. 1998. *Helicobacter pylori* infection induces gastric cancer in Mongolian gerbils. Gastroenterology 115:642–648.

245. Whary, M. T., and J. G. Fox. 2004. Natural and experimental *Helicobacter* infections. Comp. Med. 54:128–158.

246. Whitney, A. E., J. Guarner, L. Hutwagner, and B. D. Gold. 2000. *Helicobacter pylori* gastritis in children and adults: comparative histopathologic study. Ann. Diagn. Pathol. 4:279–285.

247. Wirth, H. P., M. H. Beins, M. Yang, K. T. Tham, and M. J. Blaser. 1998. Experimental infection of Mongolian gerbils with wild-type and mutant *Helicobacter pylori* strains. Infect. Immun. 66:4856–4866.

248. Wu, M. S., C. Y. Wu, C. J. Chen, M. T. Lin, C. T. Shun, and J. T. Lin. 2003. Interleukin-10 genotypes associate with the risk of gastric carcinoma in Taiwanese Chinese. Int. J. Cancer 104:617–623.

249. Xiang, Z., S. Censini, P. F. Bayeli, J. L. Telford, N. Figura, R. Rappuoli, and A. Covacci. 1995. Analysis of expression of CagA and VacA virulence factors in 43 strains of *Helicobacter pylori* reveals that clinical isolates can be divided into two major types and that CagA is not necessary for expression of the vacuolating cytotoxin. Infect. Immun. 63:94–98.

250. Yamamoto, J., S. Watanabe, T. Hirose, C. Osada, C. Ra, and N. Sato. 1999. Role of mast cells as a trigger of inflammation in Helicobacter pylori infection. J. Physiol. Pharmacol. 50:17–23.

251. Yamamoto, T., M. Kita, T. Ohno, Y. Iwakura, K. Sekikawa, and J. Imanishi. 2004. Role of tumor necrosis factor-alpha and interferon-gamma in *Helicobacter pylori* infection. Microbiol. Immunol. 48:647–654.

252. Yamaoka, Y., S. Kikuchi, H. M. el-Zimaity, O. Gutierrez, M. S. Osato, and D. Y. Graham. 2002. Importance of *Helicobacter pylori* oipA in clinical presentation, gastric inflammation, and mucosal interleukin 8 production. Gastroenterology 123:414–424.

253. Yamauchi, K., M. Tomita, T. J. Giehl, and R. T. Ellison III. 1993. Antibacterial activity of lactoferrin and a pepsin-derived lactoferrin peptide fragment. Infect. Immun. 61:719–728.

254. Yasunaga, Y., Y. Shinomura, S. Kanayama, Y. Higashimoto, M. Yabu, Y. Miyazaki, Y. Murayama, H. Nishibayashi, S. Kitamura, and Y. Matsuzawa. 1997. Mucosal interleukin-1 beta production and acid secretion in enlarged fold gastritis. Aliment. Pharmacol. Ther. 11:801–809.

255. Ye, G., C. Barrera, X. Fan, W. K. Gourley, S. E. Crowe, P. B. Ernst, and V. E. Reyes. 1997. Expression of B7-1 and B7-2 costimulatory molecules by human gastric epithelial cells: potential role in CD4+ T cell activation during *Helicobacter pylori* infection. J. Clin. Investig. 99:1628–1636.

256. Zabaleta, J., D. J. McGee, A. H. Zea, C. P. Hernandez, P. C. Rodriguez, R. A. Sierra, P. Correa, and A. C. Ochoa. 2004. *Helicobacter pylori* arginase inhibits T cell proliferation and reduces the expression of the TCR zeta-chain (CD3ζ). J. Immunol. 173:586–593.

257. Zavros, Y., S. Rathinavelu, J. Y. Kao, A. Todisco, J. Del Valle, J. V. Weinstock, M. J. Low, and J. L. Merchant. 2003. Treatment of *Helicobacter* gastritis with IL-4 requires somatostatin. Proc. Natl. Acad. Sci. USA 100:12944–12949.

258. Zheng, P. Y., and N. L. Jones. 2003. *Helicobacter pylori* strains expressing the vacuolating cytotoxin interrupt phagosome maturation in macrophages by recruiting and retaining TACO (coronin 1) protein. Cell. Microbiol. 5:25–40.